OBSTETRICAL

AND

GYNECOLOGICAL

SURVEY

Volume 3

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1948

Obstetrics

PHYSIOLOGY OF PREGNANCY, LABOR AND PUERPERIUM

REMOVAL OF THE CORPUS LUTEUM AND OF THE OVARIES OF THE RHESUS MONKEY DURING PREGNANCY: OBSERVATIONS AND CAUTIONS

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It has been known for some time that the rat, mouse and rabbit resorb their fetuses if the ovaries or all of the corpora lutea are removed at any time during pregnancy, whereas in the guinea pig it has been reported that the ovaries may be removed after the mid-period without affecting the fetuses. A considerable array of clinical cases suggests that the human ovaries are not necessary for gestation after the first few weeks.

In 1939 one of the present authors (Hartman) cited 5 experiments in which either removal of 1 ovary containing the corpus luteum of pregnancy, or removal of both ovaries, on the 95th, 89th, 46th, 35th, and 31st days respectively, did not interfere with the course of pregnancy. (Am. J. Obst. & Gynec., 37: 287, 1939.) The average period of gestation in the monkey, it will be recalled, approximates 165 days. In each of these experiments the corpus luteum was identified in the ovary at the time of operation and was subsequently verified under the microscope in serial sections.

In the present paper it is shown that the corpus luteum of pregnancy may be removed as early as the 25th day without disturbing the pregnancy. In a case described in this article, a mass of residual ovarian tissue, amounting to about ¼ of the normal bulk of the ovary, eluded discovery of 4 successive laparotomies and was only detected by postoperative section of the excised uterus. This shows how strict are the tests which must be applied in experiments such as these which depend not merely upon removal of the corpus luteum, but upon ablation of all ovarian tissue. The proof of total removal of ovarian tissue requires the cessation of cyclic phenomena (in primates, menstruation) with microscopic evidence from serial sections that the ovaries were removed intact and subsequent demonstration of the absence of residual ovarian tissue by postmortem microscopic examination.

The authors note that it would be instructive to know exactly how much earlier the corpus luteum could be removed without disturbing pregnancy. There is a well defined histological change in the corpus luteum, which begins about the 21st day and is always complete by the 25th. (Corner, Bartelmez and Hart-

man: Am. J. Anat., 59: 433, 1936.) In all probability this change marks the time when the corpus luteum ceases to be indispensable.

(If in the monkey, with a gestational period of 165 days, the 25th day marks the approximate time after which the corpus luteum is no longer necessary, the corresponding figure for the human would be about 6 weeks or around the time of the 2nd missed period. This fits in very well with clinical experience because numerous well authenticated cases are on record in which ovarian ablation has been performed in women between the 6th and 12th week of pregnancy without subsequent abortion.

There is evidence here and there, moreover, that in the human the corpus luteum may be removed even earlier than this without interfering with the successful continuation of pregnancy. Perhaps the record in this regard is the case of Pratt, as follows: He removed a corpus luteum on the 21st day after the onset of the last menstruation. The patient had come for sterility and was operated upon for retroversion and other complicating circumstances. It seemed safe on account of the recent menstruation to remove the corpus luteum for study. The patient did not menstruate in the usual 2 or 3 days following the removal of the corpus luteum but continued through a normal pregnancy and lactation. Both ovaries had been carefully inspected to insure that no other corpus luteum was present. (Am. J. Obst. & Gynec., 34: 986, 1937, in discussion of Wilson's paper.) Likewise, Essen-Möller has reported bilateral oophorectomy at 4 weeks of pregnancy followed by full term delivery 260 days after the operation. (Zentralbl. f. Gynäk., 28: 869, 1904.) It is true that abortion often follows these early oophorectomies, but it must be remembered that the pathological condition prompting the operation, such as a twisted cyst, may itself have been responsible for the accident and that the need for the corpus luteum hormone in human pregnancy—as noted by Pratt—may not be so great as might be inferred from animal work.

From a clinical viewpoint the importance of the above observations is that, in the presence of an urgent indication such as torsion of a cyst, the corpus luteum may be removed very early in human pregnancy without necessarily causing abortion. If one's hand is not forced, however, it is better to wait and remove any cyst—larger than 6 cm.—between the 14th and 18th week. Before this period the uterus appears to be more irritable and abortion from all causes is more common; while after the 20th week oophorectomy is even more frequently followed by abortion than in the first trimester, presumably because more manipulation of the uterus is entailed in the operative procedure.—Ed.)

THE TECHNIQUE OF FETAL ELECTROCARDIOGRAPHY

Solomon Hillel Blondheim

Amer. Heart J., 34: 35–49, 1947

The author presents a view of the place of fetal electrocardiography in obstetrics plus a series of cases in which the electroencephalograph has been used to record the fetal electrocardiogram. He discusses the presently limited clinical application and possible further avenues of research, recognizing that the procedures of auscultation of the fetal heart tones and x-ray of the maternal abdomen leave only a limited field of application for fetal electrocardiography.

The method used by the author begins with the patient "in supine position with low pillow under the head. Standard electrocardiograph electrodes ($1\frac{1}{2}$ x $2\frac{1}{2}$ inches) without rubber straps were coated with electrode jelly and placed on the abdomen at sites rubbed with electrode jelly and held in place with

six-inch strips of adhesive tape. The positions of the electrodes were the right and left upper quadrants and the midline at the superior limits of the uterus and the suprapubic region just above the pubic escutcheon. These electrodes were led into the terminals of a four channel push-pull amplifier type electroencephalograph by means of the usual five electrode connection wires. The three leads used routinely and recorded simultaneously were right upper quadrant to suprapubic region, midline upper abdomen to suprapubic region, and left upper quadrant to suprapubic region. The polarity was such that when the superior electrode was negative with respect to the inferior electrode, an upright deflection was recorded. The patient was allowed to rest quietly after adjustment of the electrodes for about five minutes, and then the record was standardized and recording begun. If inspection of the tracing as it was being recorded failed to reveal readily apparent fetal deflections, the placement and connections of the electrodes were rechecked, and the recording was continued intermittently at two to three minute intervals with increasing amplification. After about ten minutes the tracing was discontinued." Fetal deflections are most readily detected when superimposed on maternal P and T waves and alter the contour, as well as when they are small deflections, consistent in direction, shape, and spacing amid the baseline artifacts. Having the patient void before the test eliminates the possibility of full bladder short circuiting the fetal potential.

Of 28 tracings taken on 25 women in the last five lunar months of pregnancy, 23 or 82 per cent were positive, one tracing doubtful and four tracings were negative for deflections. Fetal and maternal heart varied independently and the sex of the fetus had no effect on the rate, the average for males being 142 and for females 143. Average voltage was found to be 7 microvolts and no increase in duration of the fetal deflection beyond 0.04 second. No significant change in rate was noted during the course of the last five lunar months of pregnancy. Bodily habitus did not seem to be an important factor in determining the incidence of negative tracings.

The various series of fetal electrocardiograms reported in the literature differ widely in technique with simplest procedures apparently giving best results. The electroencephalograph is a most sensitive instrument readily available to many obstetricians in a general hospital, gives large, easily readable tracings with all leads recorded simultaneously and low cost records immediately available after the test, and was therefore considered to be the instrument of choice. The leads have varied over the abdomen in various reports and rectal and vaginal leads have been used. The vertical and two diagonal leads are necessary since fetal deflections may appear in only one of these three leads. All abdominal leads should be referred to by letter and the superior abdominal electrodes should be placed at the upper limits of the uterus. Although the maternal deflections can be eliminated by bringing the superior and suprapubic leads closer together, they are needed to verify the presence of fetal deflections.

Fetal deflections consist of either a single sharp spike or low curve if small, or diphasic waves. The P wave is absent in records, only the QRS waves are present and the diagnosis of fetal arrhythmias is almost nullified. Direction and

amplitude are governed in part by the position of the fetal heart in relation to the electrodes, also by relative sizes of the two sides of the heart and other differences, and diagnosis of fetal position is unreliable. Many factors, such as thickness of body wall, may influence the amplitude of the fetal deflection and various drugs influence the rate. No constant relationship of maternal to fetal rate is known and arrhythmias are detected with difficulty although premature contractions and gross irregularities have been described, the latter connected with sudden interruption of pregnancy or difficulty in resuscitation after delivery.

The earliest recordings of the fetal heart were at the sixteenth week of pregnancy with sharp drop in frequency of successful recordings in seventh and eighth lunar months as compared with preceding and subsequent months; the reason for this is not apparent. Thickness of the abdominal wall, interposition of the placenta and amount of amniotic fluid are thought to influence success, while known interfering factors are other movements producing electrical potentials and aberrations in the recording system.

Clinical applications of the method are possible in cases of questionable pregnancy with positive biological test such as hydatidiform mole, or chorionepithelioma, in cases where funic or uterine souffle prevents recording of heart sounds and in diagnosis of fetal life in cases in which fetal heart sounds and movements are absent. Other applications are suggested.

(This article sets forth clearly the present status of electrocardiography in the fetus and reports a number of worthwhile observations. From a clinical viewpoint the author cites several possible practical applications of the method but at best these are few and will be needed but rarely. The author's percentage of positive readings in the last five months, namely 82 per cent, is good but reminds us that negative readings are not necessarily indicative of fetal death. Worthy of note also is the fact that his observations on the fetal heart rate, according to sex, along with much previous evidence, serve to dispel the old notion that the fetal heart rate of a boy is slower on the average than that of a girl. From the viewpoint of studying the cardiac physiology of the fetus in utero, the technique of course possesses great potentialities. For instance, what is the effect on the fetal electrocardiogram of digitalis administered to the mother?

The outstanding pioneer in fetal electrocardiography and our foremost student in the field is Erwin O. Strassman of Houston, Texas. In 1933, with Steffan, he published the first fetal electrocardiograms taken on pregnant women and in 1936 made the first report in this country on the subject. His painstaking work has been published in a series of papers, the most readily accessible being perhaps his article in the Am. Jour. Obstet., & Gynec., 36: 986, 1938. During the last 20 days of pregnancy his percentage of positive readings exceeds 90. The following uses of the fetal electroencephalogram which he cites, emphasize the great possibilities which this method possesses in the study of fetal physiology and pathology: (1) the effect of labor on the fetal heart under normal conditions; (2) the effect of labor under abnormal conditions, for example, of cranial pressure in narrow pelves; (3) the effect of all kinds of drugs, especially pituitrin, analgesics and narcotics on the fetal heart; (4) the presence of congenital deformities of the fetal heart; (5) the presence and effects of other disturbances of the fetal circulation, for example those attributable to loops and knots in the umbilical cord; (6) the presence of twins, double formations and other malformations.—Ed.)

METABOLISM OF WOMEN DURING THE REPRODUCTIVE CYCLE;
XIII. THE UTILIZATION OF NIACIN DURING LACTATION

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SOL MILLER, MARJORIE M. RUTLEDGE, HAROLD H. WILLIAMS,
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Although it has been found that niacin and choline were necessary for success-ful lactation in the hamster, little has been done to test any relation between niacin metabolism and lactation. To expand knowledge of the composition of human milk and the metabolism of women during the reproductive cycle, the present study was made of the amounts of niacin in the 24-hour intakes of food, secretions of milk and excretion of urine by 7 nursing mothers during the first ten days postpartum and by 9 women during periods of 5 consecutive days 2–10 months postpartum. Other portions of the all-over study have been previously reported.

All subjects received diets comparable in distribution but adjusted in level to meet the appetite.

With an average daily intake of 16.5 mg. of niacin the average secretion in milk per 24 hours increased from 0.04 mg. on the first day postpartum to 2.94 mg. on the tenth day. Excretion in the urine ranged from 0.92 to 0.98 mg.

The average volume of mature milk secreted per day during each of 17 5-day periods ranged from 268 to 1020 ml., with average niacin content 0.52–2.02 mg. In the urine 0.35–1.08 mg. of niacin were excreted. During 10 5-day periods the average daily urinary output of N^1-methylnicotinamide was 0.8–8.8 mg., averag-ing 4.0 mg. Of the daily niacin intakes, averages of 7 and 3 per cent, respec-tively, appeared in the milk and urine as niacin.

On good diets, no relationship is shown between intake and secretion in milk or excretion in urine, between output in milk and in urine, or between urine vol-ume and niacin content. The values for niacin in milk show a general relation-ship to milk volume rather than to intake and illustrate the wide range of normal variation in the composition of human milk from different mothers and from the same mother at different times.

The data emphasize that greater understanding of the dietary requirements of pregnant and lactating women depends on better knowledge of the physiology of milk production and secretion. Evidence indicates that the physiology of lactation is unique, and that body performance during lactation cannot be inter-preted in terms of results obtained with non-pregnant, non-lactating subjects. 2 tables.

THE INCIDENCE AND CAUSATION OF GLYCOSURIA IN PREGNANCY

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Adequate methods for the routine diagnosis and successful control of glycosuria during pregnancy have been developed within the last two decades. Investigators have established that the sugar present is glucose, not lactose as once supposed, and they tend to agree on a temporary lowering of the renal threshold of glucose, although the cause is still obscure.

The present paper is the first from a study of the incidence and causation of glycosuria, which was carried out on 540 pregnant women seen as free patients in the antenatal ward of Nowrope Wadia Maternity Hospital, Bombay, and in the out-patient clinics of that hospital and of the Hospital for Women and Children, Tardeo, Bombay. Careful histories were taken, with special attention to the diet of each patient. Specimen urine of each case was collected 3 hours after the normal midday meal, and was tested for glucose, albumin, indican, lactose and acetone bodies. Osazone tests were used to differentiate glucose and lactose fermentation.

Lactose was not found except in a very small percentage and only a few days before labor. The incidence of glycosuria showed a gradual and definite rise from month to month, as pregnancy advanced. The incidence is greater in the vegetarians than in the non-vegetarians, in cases of a calcium poor diet than in a calcium rich diet (with a difference more pronounced in the last two months of pregnancy), and is far greater in patients whose diet is poor in vitamin C than in those taking a diet rich in this factor, with an increasing difference in the last months. The incidence is also greater in subsequent pregnancies. 5 graphs.

(These findings are in keeping with general experience, namely, that lactosuria in pregnancy, except for the last 6 weeks, is uncommon, being seen in but 1 per cent of gravidae or so. As term approaches the incidence of the condition rises sharply and on the day before delivery lactosuria is demonstrable in a third or more of cases. It is most frequent and most marked, of course, in the puerperium when all women will show, on one day or another, urinary lactose well in excess of 100 mg. per cent.—Ed.)

THE RELATIONSHIP BETWEEN MATERNAL AND FETAL BLOOD CHOLESTEROL

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In this study, to investigate the relationship between the maternal and the fetal blood cholesterol, the cholesterol content in the maternal and the umbilical

blood was determined in 16 healthy, normal women in pregnancy at term, and in 8 women giving birth to twins at term. Immediately after expulsion of the fetus, while the umbilical pulse was still distinctly felt, a considerable portion of the umbilical cord was clamped between hemostats. In 6 cases the umbilical veins and arteries were separately punctured. In the remaining cases and in the twins the whole umbilical blood was taken. The total cholesterol and fractions were determined.

Results confirm reports of others that the cholesterol concentration in the fetal blood is definitely lower than in the maternal blood. Though a strict relationship could not always be observed, cases with particularly high cholesterol in the maternal blood were generally associated with respectively higher fetal cholesterol levels than were noted in cases with low maternal blood cholesterol.

No quantitative relationship existed between the values of free cholesterol and cholesterol ester. Since the ester-free cholesterol index was further found always to be different in maternal and fetal circulations, the assumption that no cholesterol ester is found in fetal blood and that free cholesterol occurs in the same concentration in both circulations was not confirmed.

Study of blood taken separately from umbilical veins and arteries failed to reveal any significant difference either in total cholesterol or in the respective free and ester fractions. Almost identical levels of cholesterol were demonstrated in separate examinations of the umbilical blood of 8 sets of twins.

All these observations support the view that fetal cholesterol is furnished chiefly by the maternal organism and passes to the fetus through the placenta, and that little if any role is played by the fetus in metabolism of cholesterol. Otherwise, fetal cholesterol level could not depend on variations in maternal cholesterol, and the concentration would be expected to vary in the arterial and venous umbilical vessels as well as in the respective umbilical circulations of twins. 3 tables.

(In the last issue of the Survey, pp. 751–753, a report by Goldwater and Stetten was abstracted in which the findings indicated that cholesterol *is* synthesized by the fetus. An editorial note appended to the abstract cited previous work which also suggested, but did not conclusively prove, the fetal manufacture of cholesterol. The contrary findings of Sadowsky and his associates reported above, namely that little if any role is played by the fetus in the metabolism of cholesterol, show that this is still a moot question.—Ed.)

MANAGEMENT OF NORMAL PREGNANCY, LABOR AND PUERPERIUM

ROUTINE CHEST ROENTGENOGRAMS IN PREGNANCY: A SUPPLEMENTARY STUDY

Hervey K. Graham

San Diego, California (from the Rees-Stealy Clinic)

In 1940 the author reported chest findings in 800 consecutive obstetrical cases. (West. J. Surg., 49: 107–112.) This study was made to detect unsuspected active or significant chest lesions in obstetrical patients and to determine the incidence of pulmonary tuberculosis in private obstetrical practice. Methods of detection were also reviewed, and x-ray examination was concluded to be the most dependable. The present report gives the roentgenological chest findings in a subsequent series of 1,267 cases, a total of 2,067 who were so examined before wartime film shortages stopped the program.

The percentage of active cases of tuberculosis dropped from 1.0 per cent in the first series to 0.6 per cent in the second, a percentage of 0.77 for the total group. Two of the 8 active cases in the second series were treated by therapeutic abortion and the others by clinical supervision and rest routine. Two who were treated by therapeutic abortion in the first group and whose disease became arrested progressed uneventfully through pregnancy this year.

Clinically important lesions were found in 3.0 to 3.6 per cent, a total of 3.44 per cent. These patients were carefully watched during and for 6 months after pregnancy. Women under pneumothorax control received pneumothorax refills within 24 hours following delivery to maintain the collapse which might be endangered by release of the pressure of pregnancy.

Evidence of old pleurisy was present in 7.45 per cent of the whole group, and of repeated respiratory infection in 9.87 per cent.

The contact cases, indicated by calcifications and occasional slight fibrosis, increased to 45 per cent in the second series as against 25 per cent in the first. This may be accounted for by a more detailed reporting of the films. It is also known that the incidence of calcification is higher in Southern California than in some other regions; furthermore, it has been reported that this incidence is high in people who react positively to intradermal testing with histoplasmin and in localities where Histoplasma capsulatum is frequently found. This may help explain the high percentage of calcifications in the present series.

In probable relation to the increased number of calcifications, the percentage of negative reports is smaller (31.9) in the second series than in the first (55 per cent).

The age range in the series is from 14 to 41 years. Most frequent occurrence of tuberculosis was in the patients in their middle twenties. This corresponds to incidence in the general population.

The U. S. and Canadian Army examinations and other surveys indicate active chest lesions in about 1.0 per cent of the general population. Most surveys of tuberculosis in pregnancy have been made among economic groups which show a higher incidence.

Use of a photoroentgen unit makes chest x-ray examination a simple procedure, and less expensive than the usual 14 x 17 films. The procedure is felt to be definitely worthwhile and justified as part of routine obstetrical care.

Dr. Frazier, in discussing the presentation, pointed out that tuberculosis in general is 4–5 times more prevalent than syphilis, and commended city and state public health mobile x-ray units, such as he has utilized in Oregon. He also mentioned histoplasmosis further as an organism which causes calcification in the chest indistinguishable by x-ray from that due to tuberculosis. Little is known about the disease except this end stage, but it apparently is not incompatible with pregnancy. 1 table.

SPINAL ANESTHESIA FOR PELVIC DELIVERY

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From the Section of Anesthesia and the Section of Obstetrics, Army Air Forces Regional Hospital, Keesler Field, Mississippi

This series of 595 cases delivered under spinal anesthesia out of 1000 consecutive cases is presented to serve a better understanding and a clearer conception of a known method.

Presentations followed average figures. There were 40 breech presentations, the remainder cephalic. Delivery in 310 patients was spontaneous. Eleven patients required cesarean section, and 679 forceps delivery, of which 562 were the prophylactic low-forceps type. In 801 cases the only premedication consisted of pentobarbital sodium, 0.2–0.5 gm. (usual dose 0.3 gm.), and scopolamine, 0.0003–0.0006 gm. (average 0.0004 gm.), given simultaneously when the cervix was dilated approximately 3 cm. In a few cases one or both drugs were repeated; no undesirable results were noted in these. Ninety-six patients received various combinations of the barbiturates, scopolamine, and narcotics such as morphine and Pantopon. The remaining 103 received no premedication either because labor was too rapid to allow for adequate preparation or because the patient entered the hospital just prior to delivery.

"As soon as the cervix is fully dilated and the patient is ready for actual delivery, she is turned on her side and held firmly by an attendant. The skin of the back is prepared with any routine antiseptic solution and 50 mg. of ephedrine sulfate with 1 cc. of 1 per cent procaine is injected locally at the contemplated site of lumbar puncture, either the third or the fourth lumbar interspace being

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fact that with it the status of gastric contents is not of vital importance; and that, as the risk is markedly increased as the dosage is increased, the reported deaths under spinal anesthesia were a result of excessive doses.

The risk of neurological sequelae exists, but should not be distorted out of proportion. There were no permanent neurological complications in this series. Others have reported there were only transient cases of nonspecific meningitis in 2 patients and of peripheral neuritis in 3 patients among 14,073 Veterans Administration patients receiving spinal anesthesia, and no permanent motor paralysis among over 10,000 patients at the Mayo Clinic.

Any method of regional anesthesia has the least harmful effect on the fetus. Effects on fetal respirations are a result of one or more of the following factors:

(1) Premedication. The use of regional anesthesia has proved that sensible, conservative premedication with the barbiturates and scopolamine has no deleterious effect on fetal respirations. Even morphine sulfate has had little influence on fetal respiration when spinal anesthesia was used.

(2) Anesthetic drug. The volatile liquid inhalation agents, the gases, and pentothal sodium can exert their influence on the fetus. 50 mg. of procaine deposited in the spinal canal has thus far demonstrated no such effect.

(3) Hypoxia. No inhalation agent permits the use of 100 per cent oxygen in the inspired mixture at all times. Nitrous oxide and oxygen is notorious for producing hypoxia and the others vary only in the extent of oxygen deprivation. This hypoxia is transmitted to the fetal brain. Cyclopropane, lacking respiratory stimulatory effect, does not ensure against hypoxia, even though a high concentration of oxygen can be given with it, and the drug can depress the fetal respiratory system, with resulting fetal anesthesia, hypoxia, and brain damage.

Only the use of regional methods of anesthesia or absence of anesthesia can ensure the least possible effect on maternal respiration. 100 per cent oxygen can be used if necessary, and routine use of oxygen is suggested during actual delivery. Spinal anesthesia was also the method of choice in all cesarean sections performed at the Army Air Forces Regional Hospital.

The satisfactory and safe employment of spinal anesthesia depends on rigid adherence to, first and foremost, the administration of a small amount of anesthetic drug, such as 50 mg. of procaine; the introduction of the drug at a low level —the third or fourth lumbar interspace; and the administration of ephedrine sulfate just prior to the anesthesia.

The only obstetrical contraindication is the decision to perform an internal podalic version. Since regional anesthesia below the tenth thoracic segment will not interfere with uterine tone or contractility, spinal anesthesia is not suitable unless larger doses are used. Deep ether is preferred for the necessary uterine relaxation in these cases.

In the authors' opinion, spinal anesthesia has these advantages in obstetrics: completely painless delivery; complete control over progress of the delivery by the obstetrician; complete relaxation of the perineum; elimination of an inhalation anesthetic and thus a lower incidence of pulmonary complications; no distortion of the perineum by injection of local anesthesia; absence of fetal depression due to

employed. The patient is then allowed to have a pain, and as soon as this has passed the spinal needle is introduced into the subarachnoid space. A syringe has previously been loaded with 50 mg. of procaine in 1 cc. of physiological saline solution. As soon as puncture is successful the anesthetic solution is injected, the needle removed, and the patient placed in position for delivery. Actual puncture and introduction of the anesthetic solution can be accomplished between two pains, and if the drug has been deposited properly within the subarachnoid space the patient will rarely have more than one pain after the injection. Blood-pressure and pulse recordings are taken, oxygen is at hand for nausea, vomiting or any other emergency, and the patient is ready for delivery. Occasionally the technic has been slightly modified to provide a so-called 'saddle spinal anesthesia' by elevation of the head approximately 10 cm. This will produce anesthesia limited almost exclusively to the lower birth canal, the perineum and the perianal region."

The ephedrine may be injected into the deltoid muscle to hasten absorption. Procaine marketed in ampules in 10 per cent solution may be used, but a 5 per cent solution is preferred for the spinal injection. The procaine locally at the site of puncture can be omitted if the patient is adequately premedicated. Larger doses of the spinal agent can be utilized but greatly increase the risks and are responsible for most of the reported fatalities.

In this series 595 patients received spinal anesthesia for pelvic delivery. In 4 (0.65 per cent) spinal anesthesia was insufficient for delivery, and local perineal anesthesia added. In 1 patient an internal podalic version became necessary after the administration of spinal anesthesia, and ether was required to produce uterine relaxation.

No fetal mortality could be attributed to spinal anesthesia. Five of the total group had delayed respiration, only one following spinal anesthesia. The "sleepy babies" delivered under spinal anesthesia were considered to be a result of premedication, but the delay was not sufficiently severe to suggest that premedication is unsafe.

There were no maternal deaths. A superficial saphenous thrombophlebitis, conservatively treated, occurred in 2 patients, and true postspinal headache in about 1 per cent. No cases of atelectasis appeared, nor pulmonary complications such as those reported with the use of inhalation anesthesia, where there is frequent vomiting and aspiration of gastric contents.

Medication with suppression of cough reflex, prolonged gastric emptying time during labor and fluidity of gastric contents, as well as the emergency nature of obstetrics, are responsible for the relatively high mortality and morbidity accompanying the use of general anesthesia for delivery. Aspiration of gastric contents and gastric lavage should be routine safeguards if general anesthesia is to be used to a depth abolishing the cough reflex. Several studies of pneumonias and deaths from this cause are referred to. In 5 deaths under spinal anesthesia reported by Norton (Am. J. Obst. & Gynec., 49: 554–566, 1945), one patient received 100 mg. of procaine and 10 mg. of pontocaine, and the other 4 were given 100 mg. of procaine. The authors believe that the crucial value of spinal anesthesia lies in the

fact that with it the status of gastric contents is not of vital importance; and that, as the risk is markedly increased as the dosage is increased, the reported deaths under spinal anesthesia were a result of excessive doses.

The risk of neurological sequelae exists, but should not be distorted out of proportion. There were no permanent neurological complications in this series. Others have reported there were only transient cases of nonspecific meningitis in 2 patients and of peripheral neuritis in 3 patients among 14,073 Veterans Administration patients receiving spinal anesthesia, and no permanent motor paralysis among over 10,000 patients at the Mayo Clinic.

Any method of regional anesthesia has the least harmful effect on the fetus. Effects on fetal respirations are a result of one or more of the following factors:

(1) Premedication. The use of regional anesthesia has proved that sensible, conservative premedication with the barbiturates and scopolamine has no deleterious effect on fetal respirations. Even morphine sulfate has had little influence on fetal respiration when spinal anesthesia was used.

(2) Anesthetic drug. The volatile liquid inhalation agents, the gases, and pentothal sodium can exert their influence on the fetus. 50 mg. of procaine deposited in the spinal canal has thus far demonstrated no such effect.

(3) Hypoxia. No inhalation agent permits the use of 100 per cent oxygen in the inspired mixture at all times. Nitrous oxide and oxygen is notorious for producing hypoxia and the others vary only in the extent of oxygen deprivation. This hypoxia is transmitted to the fetal brain. Cyclopropane, lacking respiratory stimulatory effect, does not ensure against hypoxia, even though a high concentration of oxygen can be given with it, and the drug can depress the fetal respiratory system, with resulting fetal anesthesia, hypoxia, and brain damage.

Only the use of regional methods of anesthesia or absence of anesthesia can ensure the least possible effect on maternal respiration. 100 per cent oxygen can be used if necessary, and routine use of oxygen is suggested during actual delivery. Spinal anesthesia was also the method of choice in all cesarean sections performed at the Army Air Forces Regional Hospital.

The satisfactory and safe employment of spinal anesthesia depends on rigid adherence to, first and foremost, the administration of a small amount of anesthetic drug, such as 50 mg. of procaine; the introduction of the drug at a low level —the third or fourth lumbar interspace; and the administration of ephedrine sulfate just prior to the anesthesia.

The only obstetrical contraindication is the decision to perform an internal podalic version. Since regional anesthesia below the tenth thoracic segment will not interfere with uterine tone or contractility, spinal anesthesia is not suitable unless larger doses are used. Deep ether is preferred for the necessary uterine relaxation in these cases.

In the authors' opinion, spinal anesthesia has these advantages in obstetrics: completely painless delivery; complete control over progress of the delivery by the obstetrician; complete relaxation of the perineum; elimination of an inhalation anesthetic and thus a lower incidence of pulmonary complications; no distortion of the perineum by injection of local anesthesia; absence of fetal depression due to

anesthesia; suitability for use on patients where general anesthesia is contraindicated; in general, its wide range of application.

(The employment of spinal anesthesia for delivery has grown by leaps and bounds during the last 2 years and for reasons well set forth in the above article. The authors are justified in calling attention to the fact that the barbiturates and scopolamine, when intelligently used for analgesia in the first and second stages, do not appear to inhibit respiration at birth provided no general anesthesia is employed. Still another advantage of spinal or caudal anesthesia is the sense of leisure it gives the operator in forceps deliveries. With a patient under a general anesthetic, the breathing is sometimes so labored and sterterous as to suggest that the speedier the delivery the better. Because of the absence of such worrisome signs under conduction anesthesia, the application of the blades is more likely to be painstaking and gentle, the traction smoother and the periods between pulls longer. This means of course less trauma both to mother and baby.—Ed.)

PATHOLOGY OF PREGNANCY

INFECTIOUS HEPATITIS IN PREGNANCY

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A clinical study of infectious hepatitis in pregnancy was made in 29 patients observed among 3,382 pregnant women (0.85 per cent) over a period of 32 months, extending from October, 1943 until July, 1946.

It has been shown that infectious hepatitis in pregnancy may assume 3 different clinical courses and, therefore, the authors' patients have been divided into 3 groups according to clinical severity.

(A) Hepatitis without jaundice (group A) comprising 2 (7 per cent) particularly mild cases of infectious hepatitis in which there was no clinically apparent jaundice but with transitory bilirubinuria. In these patients clinical symptoms were mild and laboratory tests showed only slight impairment of liver function.

(B) Moderately severe hepatitis (group B) was observed in 18 pregnant women (62 per cent). The pathologic manifestations exhibited by these patients resembled those observed in infectious hepatitis uncomplicated by pregnancy with, however, the following differences:

a. Insidious onset with the symptoms of the preicteric stage often misinterpreted by the patients as due to pregnancy.

b. Frequent occurrence of glossitis and angular stomatitis due to vitamin B deficiency.

c. Rare incidence of itching and bradycardia.

d. Serious functional impairment of the liver demonstrated by hypoproteinemia, positive cephalin and Takata-Ara tests, decrease of the total and cholesterol-ester blood levels and fasting hypoglycemia.

(C) Severe hepatitis with a tendency to acute atrophy of the liver (group C) was observed in 9 cases (31 per cent). The frequency of this severe form of hepatitis in pregnant women was emphasized and the following manifestations were stressed as indicative of the severity of the disease:

a. General symptoms: excessive vomiting, pronounced mental instability and subsidence of pain in the liver area.

b. Physical findings: tachycardia and progressive reduction of the liver size.

c. Laboratory findings: progressive decrease of the urea blood levels found at serial examinations, rapidly decreasing total cholesterol and cholesterol-ester blood values, persistent hypoglycemia and inadequate estrone inactivation (positive estrone clearance test). Five patients of this group died from acute atrophy of the liver.

The remote prognosis of patients recovered from infectious hepatitis in preg-
nancy was studied with the following results:

a. In 2 patients (7 per cent) chronic hepatitis resulted from infectious jaun-
dice during pregnancy.

b. Twenty-one patients showed no signs of liver function impairment
when examined 3 to 6 months after recovery.

c. No functional hepatic impairment was found in 3 women, who became
pregnant again.

Investigation of the effect of infectious hepatitis on the course of pregnancy,
labor, puerperium and on the condition of the fetus led to the following con-
clusions:

a. Hemorrhage was exceptionally rare and observed in only 2 cases shortly
before death.

b. Premature deliveries were frequent in the severe form of hepatitis.

c. Labor proceeded rapidly throughout all the stages.

d. Agalactia and hypogalactia were common in women who delivered dur-
ing the course of or shortly after recovery from infectious hepatitis.

e. The fetus was never affected by the disease of the jaundiced mother.

The following factors contributing to the particularly severe course of infec-
tious hepatitis in pregnancy were suggested:

a. Pregnancy was the decisive factor contributing to the severity of infec-
tious hepatitis.

b. State of pregnancy: all 5 fatal cases and the majority of severe cases of
infectious hepatitis were observed during the late second half of pregnancy.

c. Undernutrition: all patients who exhibited the severe form of the disease
were undernourished, their daily diet being particularly low in proteins and in
the various factors of vitamin B complex.

d. Excessive vomiting interfering with food intake.

e. Epidemic factor: all 5 fatal cases and the majority of severe cases were
observed at the time of the general increase of the disease among the general
population.

Treatment consisted in the administration of fundamental nutritional factors
(carbohydrates, proteins, essential amino-acids and vitamins) in high doses;
parenteral administration of nutrients was used in patients suffering from exces-
sive vomiting. Blood transfusions were frequently administered.

The problem of therapeutic interruption of pregnancy was discussed and the
conclusion was reached that it should be discouraged in the interest of both
mother and fetus.

The final outcome in this series of infectious hepatitis in 29 pregnant women
was as follows: Five patients died from acute atrophy of the liver (17.2 per cent).
One patient died from accidental intraperitoneal hemorrhage due to uterine rup-
ture at time of delivery. In 2 patients the disease was followed by chronic hepa-
titis (7 per cent). Twenty-one patients recovered completely (72 per cent).

Catarrhal jaundice in pregnancy is generally described as a benign disease; on
the other hand, a number of epidemics of jaundice in pregnancy with a very high

mortality (92 per cent) have now been reported. These two forms of jaundice have been considered as two different diseases until recently, when it was established that both are due to the same icterogenic virus of infectious hepatitis. In the light of this discovery the benign "icterus catarrhalis" and the extremely serious epidemic jaundice in pregnant women should, in the authors' opinion, now be considered as the same disease.

The early diagnosis of the disease and intensive treatment from its very inception seem of great importance. Unfortunately, the diagnosis is particularly difficult in the early, preicteric stage. One must be particularly cautious in the diagnosis of infectious hepatitis in pregnant women, since general symptoms characteristic of the preicteric stage, e.g., anorexia, nausea and vomiting may be induced by pregnancy without hepatic involvement. The routine urinalysis for bilirubin in all pregnant women at times of epidemics is very helpful. Following its introduction in their Centers of Prenatal Care, two cases of hepatitis without jaundice and two others in the preicteric stage were detected. The diagnosis of infectious hepatitis may become very difficult, if jaundice develops during the pernicious vomiting of pregnancy.

In the diagnosis of infectious hepatitis the possibility of spirochetal jaundice (Weil's disease) should be considered. It is noteworthy that during epidemics of infectious hepatitis there may be concomitant epidemics of spirochetal jaundice.

In this study of 29 pregnant women with infectious hepatitis the symptoms which indicated the danger of acute atrophy of the liver before hepatic coma set in are described. The finding of a progressive decrease of the urea blood level was a most valuable sign of the severity of the disease and has been found in all their five fatal cases as well as in three other very severe instances. It might seem surprising that the depression of urea synthesis, considered a most essential and less vulnerable hepatic function, figured as their most important laboratory sign of the severity of infectious hepatitis in pregnancy. In fact, it was found in animal experiments that $\frac{4}{5}$ of the liver may be removed without a significant effect on urea synthesis (Mann, F. C. and Bollman, J. L.: Arch. Path., 1: 681, 1926.) Furthermore, liver damage frequently induced a rise of the blood urea level, and only in exceptional cases was a decided lowering of the urea level observed. However, the authors found in their cases a sudden drop in the blood urea value may occur before clinical signs of aggravation of the disease appear. In all their five fatal cases lowering of blood urea level preceded by several days the appearance of hepatic coma. This observation lead them to the conclusion that a progressive decrease of the urea blood level was a more useful indication of the severity of infectious hepatitis in pregnancy than any other liver function test. Furthermore, inadequate estrone inactivation (positive estrone clearance test) may serve as a sign of poor prognosis. The intensity of the icteric tint is not an important sign pointing to the severity of infectious hepatitis. In fact, no relationship could be found between the severity of the clinical course and the depth of the jaundice. Numerous cases of intense jaundice with an icterus index of 300 and without particularly serious hepatic functional impairment were observed. On the other hand, 4 of 5 patients who died from acute atrophy of

the liver presented deep icterus (icterus index 300 at its peak value), while in the fifth case jaundice was never particularly deep (icterus index 100 at its peak value). It seemed also surprising that although hemorrhages frequently appear in serious liver diseases, they did not occur in their patients, except in 2 cases shortly before death. Furthermore, the prothrombin time, considered a sensitive test of liver damage, was normal in all their cases during the icteric stage, and became prolonged only in the 2 above mentioned cases in hepatic coma.

In the study of the factors leading to acute liver atrophy in pregnant women with infectious hepatitis, special attention has been attached to the role of undernutrition. It seemed that undernourished pregnant women with a daily intake especially low in proteins, were particularly apt to develop acute atrophy of the liver as a complication of infectious hepatitis. Consequently, a well balanced diet, rich in proteins, is to be recommended to all pregnant women living in areas of epidemics of infectious hepatitis. The therapy in severe cases consisted chiefly of intravenously administered protein and glucose. The authors frequently used blood transfusions successfully in these cases, although the use of whole blood in liver diseases was generally discouraged.

(This paper is probably one of the most important published in 1947 because it brings to light a new concept and documents it with convincing evidence. The new conception is, of course, that the idiopathic acute yellow atrophy of gestation is actually infectious hepatitis in fulminant form. Most pathologists would now agree on this point, I believe. For instance, the preëminent authority on the pathology of infectious hepatitis, Lieut.-Col. Balduin Lucké, who has described his extensive war experience with the disease in a series of classic monographs, writes as follows: "The present studies leave little doubt that idiopathic yellow atrophy represents the end stage of epidemic hepatitis" (Am. J. Path., 20: 471–593, 1944; see also same journal, 22: 867–945, 1946). Although obstetricians may call to mind a number of possible objections to the hypothesis advanced in the above abstract, a careful study of that paper as well as those of Lucké will go far to convince them that the two conditions are one.—Ed.)

INFECTIOUS HEPATITIS ASSOCIATED WITH PREGNANCY: A REPORT OF FOUR CASES

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An epidemic of infectious hepatitis began among the civilian population of Portland, Maine, during 1944, and has continued to date. Four cases occurred in pregnant women. Since this combination is rare, having occurred in only 10 of 72,000 pregnant patients at the Chicago Lying-in Hospital, the 4 cases are presented in detail.

The first patient contracted infectious hepatitis in the second trimester of pregnancy. Intense jaundice persisted, and there was evidence of liver damage. Following the start of therapy there was some improvement over 2 months.

When treatment was stopped there was evidence of further deterioration, and it was decided to interrupt the pregnancy. Cesarean section was performed at about the 7th month. The baby died from causes probably not associated with the hepatitis. After the section there was clinical and chemical improvement which cannot be attributed specifically to any therapy given. Seven and a half months after discharge there was still an elevated sedimentation rate and altered blood protein, some permanent liver damage presumably being indicated. The total period of jaundice was approximately 130 days.

The second patient contracted hepatitis late in the second trimester of pregnancy, showed definite evidence of liver dysfunction, and was delivered at $6\frac{1}{2}$ months of a normal baby who lived. Improvement began soon after delivery. Before discharge the patient showed a complete clinical recovery, all laboratory tests having returned to normal except for a high sedimentation rate. She did not return for follow-up studies, so that no statement can be made regarding permanent liver damage, although it seems unlikely. The jaundice lasted approximately 30 days.

The third case might strictly be excluded from the series, since symptoms of hepatitis first appeared about 31 days after a miscarriage, occurring at the end of the first trimester. Since the incubation period is from 20 to 40 days, however, it is evident that infection occurred at about the time of, or perhaps even before, the miscarriage. Whether the hepatitis was directly related to the miscarriage cannot, of course, be determined. After a month of jaundice, therapy was started. Although treatment was not so intensive as they should have wished, some improvement began about 3 weeks after admission and continued until no evidence of liver damage was apparent. The total duration of jaundice was 80 to 85 days.

In the fourth case the patient, when about 28 weeks pregnant, had had a shaking chill and had rapidly developed fever, sweating, headache, nausea, vomiting, severe pains in the lower back and lower abdomen and pain on moving the eyes. Four days later clay colored stools, biluria and jaundice developed with an icterus index of 50. The jaundice persisted 23 days. Spontaneous delivery occurred shortly after the expected date of confinement, the child as well as the subsequent course of the child being normal.

There is remarkably little in the literature on the concurrence of infectious hepatitis and pregnancy, to which Beck refers as catarrhal jaundice, a condition that is seldom seen in pregnancy. DeLee states that pregnant women show a high mortality in hepatitis. Stander considered "the catarrhal variety" of jaundice in pregnancy to be without significance and to undergo spontaneous cure, but subsequently referred to "epidemics of jaundice . . . in which the disease . . . was disastrous in pregnancy." In the latter report there were many maternal deaths, abortions and premature deliveries.

Saurer (Monatschr. f. Geburtsh. u. Gynäk, 115: 16–33, 1943) reported 5 cases of hepatitis in pregnant women occurring during 1942 and 1943. Four were multiparas ranging in age from 24 to 37 years. One had a premature delivery at 5 months and later developed symptoms of hepatitis, as in Case 3 above.

This was apparently the only premature delivery. There were no maternal deaths and no other fetal deaths. Only one woman, who had delivered at term during the pre-icteric stage of hepatitis, had a prolonged period of jaundice. In this case the jaundice lasted about 3 months.

It is impossible to draw definite conclusions from this small series of cases. There were no maternal deaths, and the 2 deaths in the children could be attributed only to the prematurity, not to the maternal hepatitis. In only one woman, however, did both the pregnancy and the hepatitis pursue normal courses. Two patients had premature labors, 1 required termination of the pregnancy, and 2 had prolonged periods of jaundice. The patient in Case 1 may have suffered permanent liver damage, since when last seen she still had an elevated sedimentation rate and an abnormal blood protein level. Permanent damage seems definitely ruled out in Case 4 and unlikely in the other 2 cases.

It seems safe to conclude that the danger of maternal death from hepatitis is small. The chance of an uneventful pregnancy is poor, however, and the possibility of prolonged jaundice and perhaps permanent liver damage in the mother is present. Since improvement in the mother occurred soon after the cesarean section in Case 1 and soon after delivery in Case 2, it appears that the mother benefits from removal of the fetus. Pregnancy itself may place an extra strain on an already diseased liver, and in severe cases of hepatitis interruption of the pregnancy should be seriously considered unless the patient improves rapidly under observation.

ECLAMPSIA

THE INTERNATIONAL CONGRESS, ROTUNDA BICENTENARY

Rotunda Lying-in Hospital, Dublin

Lancet, 2: 102–103, 1947

This discussion of eclampsia begins with the statement by Dr. Falkiner that whereas mortality from sepsis is declining, mortality from eclampsia, preeclampsia and toxic albuminuria is virtually unchanged. These conditions, manifestations of a single disease, might end in spontaneous delivery or progress to convulsions. Present treatment then is based upon belief that labor accentuates the disease, that control of convulsions is beneficial, that shock is dangerous and that delivery without shock will lead to recovery unless there have been irreversible changes in brain, liver, or kidneys. Rotunda routine treatment involves use of morphine, magnesium sulfate (up to 8 gm. in 12 hours), and intravenous glucose. If the patient is not in labor, and response is satisfactory, no obstetric interference is undertaken; but if fits are uncontrolled, or coma is extreme, cesarean section under gas and oxygen is indicated. With a patient in labor making normal progress, normal delivery in the second stage is performed, with the utmost care. Where labor is complicated by inertia and the condition

is deteriorating, cesarean section is considered; and in all cases with dystocia associated with delay and probable difficulty at delivery, it is demanded. Pre-eclampsia might be an urgent indication for section. In 1941–47, 93 cases had been treated with a loss of 8 mothers and 16 infants. Of the 16 women having cesarean section 2 had died (1 moribund on admission, 1 cerebral hemorrhage), with 1 fetal death.

Prof. H. J. Stander summarized suggested causes of eclampsia as follows:

A. Causes Outside Maternal Organism
   1. Dietary deficiency: (a) general, (b) protein, (c) calcium, (d) vitamin.
   2. Infection: (a) pyelitis, (b) septic foci to infect placenta.
   3. Meteorological influences.
B. Causes Within Maternal Organism
   1. Constitutional predisposition.
   2. Pressure.
   3. Endocrine imbalance: (a) pituitary, (b) adrenal cortex, (c) others.
   4. Chemical poisons: (a) guanidine, (b) histamine, (c) tyramine.
C. Causes Within Products of Conception
   1. Placenta: (a) infarct, (b) ischemia, (c) crush syndrome, (d) allergy, (e) elements.
   2. Fetus: (a) endocrine imbalance, adrenal cortex, (b) iso-immunization (1) Rh factor, (2) other factors.

In groups A and B he thought further attention should be given to dietary deficiencies, endocrine imbalance, and chemical poisons. He referred to the Smiths' discovery of a toxic euglobulin in menstrual discharge and in the blood-stream of menstruating and toxic women. Toxemia late in pregnancy might prove to be due to withdrawal of endocrine support, owing to interference with the blood-supply of the placenta. Many theories came to involve the placenta and usually something outside the placenta was supposed to cause the placental changes; but it was not clear at what stage of events the placenta was implicated. Iso-immunization could probably be ruled out. What was needed now was more data.

The role of the placenta, which initiates and sustains hyperplasia of pituitary, thyroid, and adrenal cortex, was emphasized by Hofbauer. He regards eclampsia as a response by sensitized vessels to pressor substances present in normal blood. Painful stimuli of splanchnic areas lead to increased output of these substances, and termination of labor can be considered a physiological lumbar sympathectomy.

Others stressed interference with placental function by compression of the intervillous spaces (e.g., in multiple pregnancy), and correlated eclampsia with geographical differences such as climate and soil calcium. The primary emphasis, however, was placed on diet. The effects of food deficiencies and of over-rich diets were presented from various points of view. For example, at the Brussels Hospital the incidence of pre-eclamptic toxemia, which was 2.09 per cent in 1938–1940, fell to 0.70 per cent in 1941–1942, rose to 0.87 per cent in 1943–1944 when more food was obtainable on the black market, and went up to 4.01 per cent in 1945–1946 after the liberation. In Hong-Kong the incidence

of pregnancy toxemias rose with the incidence of beriberi, and both fell after the surrender.

Proper antenatal care and timely admission to the hospital were also urged. Irving discussed the treatment of the antepartum eclamptic during fits. At the Boston Lying-in Hospital patients were given morphine, magnesium sulphate, and "Veratrone." The anticonvulsive effect of veratrone was probably due to vasodilatation and relief of cerebral edema, and it was given at 20-minute intervals to keep the blood-pressure below 150. Some 24–72 hours after convulsions ceased, labor was induced by rupture of membranes or by a dilating bag, and was allowed to continue naturally. Cesarean section was reserved for cases with other indications such as disproportion. Opinion on the use of veratrone was divided, however. A statistical approach seems needed.

THE HEART IN TOXAEMIA OF PREGNANCY

PAUL SZEKELY AND LINTON SNAITH

From The Cardiovascular Department and the Department of Obstetrics, Newcastle General Hospital, Newcastle-upon-Tyne, England

Although acute pulmonary edema is a recognized complication of toxemia of pregnancy, its mechanism is incompletely understood. In some of the reported cases the clinical picture was similar to that of cardiac asthma and the cause of the pulmonary edema was thought to be left ventricular failure. Detailed studies of the heart in toxemia of pregnancy, however, have been few, and reports showing that toxemia of pregnancy may be associated with myocardial damage are not many.

The present paper is based on the observations made in 19 unselected cases of toxemia of pregnancy, delivered in the Department of Obstetrics of the Newcastle General Hospital. Although the difficulty of assessing the severity of the toxemic state is fully recognized, an attempt has been made to classify the cases for the purposes of this study. The majority were classified as severe, the criteria being subjective symptoms, such as headache, vomiting and visual disturbance, and height of blood pressure, edema, albuminuria, and the occurrence of eclamptic fits. All the "severe" cases had a blood pressure of more than 160/100, in addition to other symptoms and signs of toxemia, except one with a blood pressure of 130/95, classified as severe because of eclamptic convulsions.

Clinical and cardiographic studies were made in all and, in addition, radioscopic examination in 9 cases. A total of 7 cases were thought to show significant clinical and/or cardiographic changes. Left ventricular failure was observed in 3 and the first of these also showed T wave changes similar to those seen in anterior myocardial infarction. Significant cardiographic changes were seen in 5, these changes consisting of transient alterations of the T waves

usually in both standard and chest leads. Cardiographic changes of doubtful significance were observed in 6 others. In the remaining 8 the cardiograms were within normal limits. Sinus tachycardia was frequent and extra-systoles were observed in 2.

It would appear from these observations that gross cardiac enlargement is not a feature of pure "toxemic" cardiac lesion, irrespective of the presence or absence of cardiac failure. Only one of the authors' cases showed enlargement of the left ventricle. It is true that the radioscopic examination in many of their cases was not carried out at the height of the disease; nevertheless, the clinical impression as a rule was that of a normal-sized heart. If gross cardiac enlargement is present, it probably indicates either antecedent hypertension or heart disease not "toxemic" in origin. There is nothing to suggest that peri-cardial effusion is present in toxemia of pregnancy to account for the cardiographic changes or the heart failure.

Although convincing proof is still lacking of a direct damage to the myocardial vessels in toxemia of pregnancy, in the light of the above-mentioned clinical and anatomical findings the possibility of structural damage to the small coronary branches cannot be excluded with certainty. There appeared to be no close correlation between the severity of the toxemic state and the degree of cardiac damage. The duration of the toxemia may be more important than its severity in producing the cardiac damage.

The true significance of the observations presented in this paper lies in showing that cardiac involvement is not uncommon in toxemia of pregnancy. The authors believe that some of the cases of acute antepartum or postpartum cardiac failure of undetermined etiology may be instances of toxemia, even if the recognized signs of the latter condition are not convincingly present at the time of the onset of the cardiac failure; and that some of the cases of vascular collapse known as "obstetric shock" may be instances of true toxemia. The clinical picture of postpartum vascular collapse in one of their cases was identical with that of so-called "obstetric shock." Most such cases are associated with traumatic delivery and postpartum loss, and the chief causative factor is blood loss. There remain, however, those infrequent but important cases where collapse occurs with minimal loss after labor and delivery. Such cases may be instances of toxemia of pregnancy with associated myocardial damage.

(In 1946 Wallace, Katz, Langendorf and Buxbaum examined the electrocardiographic records of 12 patients suffering from toxemia and found significant changes in 6, with actual left ventricular failure in 2 of these (Arch. Int. Med., 77:405, 1946; abstracted with editorial note in Survey, 1: 630, 1946). They felt that the alterations simulated those occasionally seen in acute nephritis and attributed them to focal myocardial necrosis, infiltration or edema rather than to myocardial infarction secondary to occlusion of the coronary artery. In the above paper by Szekely and Snaith we have another article on this subject, also from extremely competent observers, which reports almost identical findings. Moreover, clinical and autopsy evidence tends to support these observations.

What is the truth about this question,—a question with sweeping clinical implications of the utmost practical importance? It is indeed beginning to appear that we may have been overlooking all these years one of the vital aspects of severe pre-eclampsia and eclamp-

of pregnancy toxemias rose with the incidence of beriberi, and both fell after the surrender.

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The second view, on the other hand, holds that all inevitable and incomplete abortions which are not rapidly and spontaneously completed should be treated by surgical evacuation of the uterus. While this of course requires many fewer hospital beds, since the stay in hospital is relatively short, the authors believe that in principle and in practice it is also at least as safe as the conservative treatment.

In surgery it has long been accepted that a wound heals most rapidly if cleared of non-viable debris. The wound at the placental site, on the other hand, has been credited with unwarranted physiological properties. It has no magical powers of rapid healing when its surface is covered with necrotic debris; there is even the probability of secondary infection from this retained material.

The "interventionist" attitude has therefore been adopted at Radcliffe Infirmary, Oxford, and continued for eight years. The series now analyzed consists of 600 consecutive cases, 500 on general wards and 100 in private beds, treated surgically there. (Fifty-eight cases of threatened abortion, spontaneous complete abortion, and missed abortion are not included.) Forty-two patients were frankly septic on admission, 2 from a generalized Clostridium welchii infection. Many were in critical condition from extreme blood loss. When necessary, the patient was given resuscitative measures in the casualty admitting room and then taken direct to the operating theater. Avoidance of unnecessary handling at this stage can be life-saving. On 71 occasions blood transfusion was administered, always started before taking the patient to the theater and usually continued during operation; thus the exsanguinated patient was better prepared for operation, the risk of early transfusion reactions being masked by anesthesia was reduced, and in the unlikely event of further extensive blood loss there was a minimum delay in replacing it. Rh-immunization is now avoided by preliminary testing, or in extremely urgent cases reduced to a minimum by use of Rh-negative blood. When the patient was suffering from extensive blood loss or shock, it was often necessary, because of venous spasm, to give the blood under pressure. When sepsis was present chemotherapy was begun, 2 g. of a sulphonamide as an initial dose followed by 1 g. four-hourly. If hemorrhage was severe the patient was taken to the theater without further delay; otherwise operation was postponed 12–24 hours so as to obtain a satisfactory blood concentration of the drug.

Once the patient was considered fit for operation, treatment was as follows. After preliminary shaving and washing of the vulva and catheterization, the patient was taken to the theater with the transfusion still running. In critical cases the anesthetic was not started until the surgeon was gowned and ready to operate. Early in the series ether was used extensively, but this was replaced by hexobarbitone and then by thiopentone, as being less disturbing to the patient. Small doses, often only 0.25 g., were used. After the vulva and vagina had been swabbed with flavine in spirit, 1 in 1,000, the surgeon gently examined the pelvis to determine the exact position of the uterus and the state of the cervix. Failure to make this preliminary examination can result in the soft wall of a pregnant retroverted uterus being perforated by sound, dilators, or forceps.

sia, namely, an especial tendency to cardiac failure. It is true that digitalization has been recommended (Stroganoff) and practiced widely in these cases, but largely on an empirical basis, and myocardial changes have never been stressed. However, as indicated in the editorial note cited above, there is substantial evidence on the other side of the question— that is,. against frequent myocardial involvement—and further observations are urgently needed.—Ed.)

THE TREATMENT OF INEVITABLE, INCOMPLETE, AND SEPTIC ABORTION

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According to the authors, abortion is the most common serious complication of pregnancy, with an incidence of probably 25 per cent. Carrying a mortality of 100 per cent for the fetus and grave risks for the mother, it causes greater wastage of potential and actual citizens than any disease. It has been estimated that 700,000 infants and 3500 mothers die annually in America as a result of abortion. Although evidence suggests a high incidence of fetal deformity in these cases, the loss of potentially healthy citizens is none the less great.

The purpose of this paper is to consider treatment, once abortion has become inevitable, incomplete, or septic. The following criteria were accepted for diagnosis: (1) An abortion was considered inevitable when bleeding was associated with uterine contractions and dilatation of the internal ostium. (2) An incomplete abortion was diagnosed when bleeding persisted following the abortion and examination revealed a bulky uterus, usually with a patulous cervical canal, or when it was known from the material passed that placental tissue had been retained. Subsequent removal or passage of placental fragments confirmed the diagnosis. (3) An abortion was considered septic when it was associated with pyrexia for which no other cause was found, offensive or purulent discharge, or evidence of pelvic inflammation. Cases of pyrexia during the process of spontaneous evacuation of a uterus with no preceding or subsequent evidence of uterine, pelvic, or general infection were not included.

The recognized immediate dangers to the mother are death or serious illness as a result of hemorrhage or infection. In Great Britain and America it is estimated that 21 to 25 per cent of maternal deaths are due to abortion.

Two main schools of thought exist concerning the treatment of inevitable or incomplete abortion. According to the first view, if left alone the uterus will ultimately empty itself, and if it is allowed to do so the mother is subjected to the least possible risk. Some advocates of this attitude believe the mortality is twice as high with active as with conservative treatment. These results, however, were obtained before the days of specific chemotherapy. This treatment also requires many hospital beds, for it may take several weeks for completion.

reduces length of stay in hospital. The low mortality may be attributed to the method of treatment and to the fact that a team skilled in handling these cases was responsible for them.

(As the authors point out, the old controversy over radical vs. conservative management of infected abortions has been put in a new light through the advent of chemotherapy. Although Corston and Stallworthy state that the "interventionist" attitude has been adopted at the Radcliffe Infirmary, it will be noted that they only intervene after 12–24 hours of chemotherapy unless forced to do so by hemorrhage. This may be regarded as a sort of modification of the radical treatment based on the known bacteriocidal action of penicillin and the sulfonamides. Our own management of infected abortions has long been one of non-intervention, unless our hand is forced by bleeding, and on retrospect we have found reason to regret this policy. Until recently no intra-uterine manipulation has been carried out until the patient has been afebrile for 5 days, but during the past few years, with intensive chemotherapy from the moment of admission, this interval has been reduced to 2 days with no untoward results. We still do not intervene in the presence of fever unless hemorrhage makes it mandatory.—Ed.)

RETRODISPLACED GRAVID UTERUS

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Brit. Med. J., 1: 169–172, 1947

The author reviews 66 cases of women with retrodisplaced gravid uteri admitted to wards of University College Hospital since 1928 because of various conditions including threatened abortion, hyperemesis gravidarum, incarceration of the uterus, or for purposes of observation. Other articles have shown in one study an incidence of retrodisplacement of 20 per cent in nullipara, in another, an analysis of 2000 cases, an incidence of 18 per cent in nullipara, 35 per cent in postpartum women. Of 474 patients seen in the antenatal department of this hospital at about the 12th week of pregnancy the incidence of retrodisplacement was 5.5 per cent for primigravidae, 6.5 per cent for multiparae.

The author reviews his cases in terms of treatment of the retrodisplacement. He finds that a conservative approach is indicated and surgery should be withheld. In cases of sterility he finds that the ordinary approach and treatment given to patients are indicated and that only after tests of tubal patency, etc., prove not to be efficacious should treatment of the retrodisplaced uterus be considered.

Abortion occurred in one-third of the cases hospitalized and in other series occurred in 1 out of 13. The usual incidence as quoted by the author is 1 in 5 for all pregnancies. He finds that the retrodisplaced uterus which is inclined to abort does so even after anteversion. In two of his cases abortion occurred and both patients later carried pregnancies to term without operation. In another case the patient had been pregnant 9 times and aborted 7 times, delivered prematurely twice, despite successful manual anteversion in each preg-

If the canal was patulous and placental tissue was within reach it was gently removed with the gloved finger. If not, then the cervix was exposed and an oxytocic drug was injected under vision into the cleaned cervix. Early in the series 0.5 ml. of "pituitrin" was used, but this was later abandoned in favor of 0.5 mg. of ergometrine, because of the generalized pallor and occasional sweating associated with the use of pituitrin and rare but unnecessary fatalities when used in obstetrics. The length of the uterine cavity was gently measured with a sound. Unless it was already patulous, as was often the case, the cervical canal was carefully dilated to the size of a No. 14–16 Hegar dilator. Sponge forceps were then carefully introduced, opened, rotated through 90 degrees, closed, and withdrawn, repeatedly, until no further pieces of placental tissue were removed in this way. The cavity was then gently and thoroughly explored with a blunt flushing curette through which passed a slow stream of dettol (2 dr. to 1 pint—7 ml. to 568 ml.) at a temperature of 110°F. (43.3°C.). This removed small fragments of tissue missed by the forceps and also stimulated uterine contractions, as shown by the rapid decrease in the length of the uterine cavity and the cessation of any bleeding. The cavity was then packed with a sterile 2-inch (5-cm.) gauze roll, which was removed six hours later. In septic cases the pack was impregnated with 10 g. of sulphathiazole powder. This pack serves a dual function. By promoting uterine contractions and by direct pressure on the placental site it safeguards against further bleeding during recovery from anesthesia, and with its removal it clears any small fragments or clot which if left could promote discharge, further hemorrhage, and possibly infection. Following removal of the pack there was rarely more than a slight stained discharge, which usually ceased within 48–72 hours of the operation. The patient was allowed up 36–48 hours later, and if home conditions were satisfactory was discharged on the third or fourth day. An attempt was made to discover the cause of the abortion, and advice was given on the necessary care during the early weeks of a subsequent pregnancy. Iron was given to combat anemia secondary to the blood loss, and the patient was requested to report for a follow-up examination in a month.

There was one death (a mortality of 0.17 per cent) in the series: one of the two patients whose abortion was complicated by a generalized Cl. welchii infection. Considered moribund on admission, this patient had aborted one month previously and had daily hemorrhage since. At time of admission the hemoglobin level was 22 per cent, and patient was in a state of collapse. A provisional diagnosis of gas gangrene infection was made, and treatment was instituted with serum in addition to transfusion and chemotherapy, pending the bacteriologist's report. Death occurred within 24 hours of admission. Necropsy confirmed the presence of Cl. welchii septicemia.

As already stated, patients with suitable home facilities were commonly discharged on the third or fourth day. The average length of stay was 7.5 days for the 500 non-private patients.

Surgical evacuation of the uterus in inevitable, incomplete and septic abortion, if carefully performed, provides a safe and efficient method of treatment, and

FURTHER OBSERVATIONS ON POLIOMYELITIS IN PREGNANCY

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The total number of recorded instances in which pregnancy complicated poliomyelitis or poliomyelitis complicated pregnancy is well over 175. Data from 1945 and 1946 epidemics indicate that of 24 married women admitted to the South View Isolation Hospital with a diagnosis of poliomyelitis, 14 were pregnant.

These data, as well as several reports on the subject, indicate that the pregnant woman is apparently more susceptible to the poliomyelitis virus than the non-pregnant woman. The previous paper by Fox and Sennett (Am. J. M. Sc., 209: 382, 1945) cited several reports in the literature which supported the thesis that the endocrine glands influence susceptibility or resistance in some way as yet not fully understood. Numerous references can be made to glandular changes which occur in pregnancy, and, as pregnancy progresses, to the effect of the fetal ductless glands on the maternal metabolism; but more specific citations can be made. The theory that the endocrine glands can influence susceptibility to poliomyelitis receives support from Jungeblut and Engle (J. A. M. A., 99: 2091, 1932; J. Immunol., 24: 237, 1933), who believe that immunity in this disease is dependent upon physique and physiologic mechanisms such as menstruation and pregnancy. However, their work, indicating that the immune body content of the sera varied with the menstrual cycle, has been opposed by the more extensive studies of Hudson, Lennethe and King (J. Exper. Med., 59: 543, 1934). Jungeblut and Engle found that after adrenalectomy the sera of certain monkeys failed to neutralize the virus. After treatment with cortical hormone, the neutralizing power returned. Adrenalectomy caused the disappearance of the natural poliomyelitis antibody, but the antibody present in animals recovered from the infection did not disappear. For such cases Aycock introduced the term "autarcesis," the power to resist infection. This quality is inherent in the normal physiologic function of the body. While he admits that immunity following contact with the virus is important, he stresses the role of normally changing physiologic imbalance in causing increased susceptibility to infection. The multiple physiologic changes occurring in pregnancy make it seem not unlikely that differences in susceptibility are encountered between the gravid and non-gravid state, which make the gravid patient more susceptible.

Several groups of workers have attempted to determine whether poliomyelitis runs an unusually fatal course during pregnancy, but the evidence cannot be regarded as conclusive. Others have presented evidence that the prognosis is bad for mothers contracting poliomyelitis in the last trimester. This issue also

nancy.   The author recommends that abortion be considered as habitual abortion despite the presence of retrodisplacement.

Incarceration of the uterus occurred in 10 patients—3 primigravidae and 7 multiparae—and was indicated by sudden onset of retention of urine, accompanied by lower abdominal pain.   Occasionally this was preceded by painful and frequent micturition for several days.   In this series incarceration occurred as early as the 13th week of pregnancy, as late as the 17th week.   Sacculation occurred in 3 cases and was treated once by cesarean section, again in the same patient by manual anteversion, and in the other patient resulted in abortion at 19 weeks.   Retention of urine in incarceration of the retrodisplaced uterus is considered by the author to be due to elongation of the urethra and mechanical pressure upon the weakened urethra from the pelvic contents.

More than half the patients in this group who were followed, 9 of 16, had an anteverted uterus at 8 weeks postpartum and can be considered "cured" of the retrodisplacement.

In order to prevent incarceration of the retrodisplaced uterus the author recommends passive postural treatment such as sleeping in Sim's position or prone prior to 12th week.   After this a large watch spring rubber pessary may be inserted into the vagina and further postural exercises including knee-chest position for several hours daily be prescribed.   Any difficulty with micturition must be treated and, if incarceration occurs, then continuous catheterization, postural treatment and, if necessary, manual reposition and insertion of pessary to maintain position of anteversion.   Urinary antiseptics are indicated in all such cases.

(Unless the 66 patients in this report represented a very selected group, the incidence of incarceration, namely 1 in 7, is extremely high.   I see a case but once every 2 or 3 years and, even if we consider only gravidae with retrodisplaced uteri, I should think that the incidence of incarceration would be nearer 1 in 700 than 1 in 7.   The infrequence of incarceration of the retroposed gravid uterus would seem an important point to stress since, if the incidence of the complication were anything like as high as the above figures would suggest, active interference in all cases of retrodisplacement in pregnancy would be advisable.

Actually, in my opinion at least, interference in the form of replacement with pessary insertion, etc., is rarely indicated since almost all these cases will undergo spontaneous restitution prior to the 12th week.   As the author shows, incarceration is a phenomenon of the 13th to 17th week, so there is no reason to worry about this before the 12th week. In regard to the threat of abortion as the result of the retroposition, no convincing figures have been presented, as far as I am aware, showing that abortion is any more common in these patients than in women with normally placed uteri.   It is my custom to do nothing with retroposition during the first trimester except possibly knee-chest position night and morning, and to carry out manual replacement only if urinary symptoms develop or if the condition persists after the 12th week.   If this policy is pursued the occasion for manual replacement will rarely present itself; nor do I believe that the abortion rate will be any higher than with manual reposition.   In this connection, it seems to me that our text-books, most of which recommend manual replacement and a pessary as soon as the diagnosis is made, might advisably veer to a less active policy in this complication.—Ed.)

have noted that the incidence of poliomyelitis in pregnancy varies according to the stage of pregnancy, and recorded in 70 cases the following incidence:

1st third of pregnancy........17.1 per cent
2nd third of pregnancy........34.3 per cent
3rd third of pregnancy........48.6 per cent

In experiments in pregnant cotton-rats they demonstrated that of 13 animals in the first third of pregnancy 3 were resistant to the virus, whereas 51 animals in later pregnancy all developed the disease after three-way inoculation of virus (intracerebral, intranasal, and subcutaneous).

Most writers consider that poliomyelitis has no adverse effect on pregnancy or labor. (Brahdy and Lenarsky: Ibid, 101: 195, 1933; Kleinberg and Horwitz: Surg. Gynec. Obstet., 72: 58, 1941.) The exceptions to this rule when applied to pregnancy are to be found in cases of widespread paralysis in the mother, in which case death of the fetus in utero from asphyxia is the obvious risk. (Harmon and Hoyne: Ibid, 123: 185, 1943.) Aycock and Ingalls (Amer. J. Med. Sci., 212: 366, 1946) have collected records of the fate of the fetus in 131 cases; in 25 cases the baby was stillborn or died shortly after birth; and in 6 cases abortion occurred in the first three months.

That the uterus has an independent nerve-supply is shown by the fact that normal contraction occurs after transection of the spinal cord or after experimental division of the sympathetic nerve-supply. (Wright, S.: Applied Physiology, London, 1940.) Moreover the ability of the uterus to expel its contents has been observed also in cases of cord tumor and fracture with cord involvement. In 243 cases pregnancy has taken place within a year of the onset of poliomyelitis; normal and uneventful pregnancies and labors were experienced in all cases. (Kleinberg and Horwitz: Surg. Gynec. Obstet., 72: 58, 1941.)

There is therefore strong evidence that pregnancy and labor should not be interfered with except for complications operative for all pregnant women. While both termination of pregnancy and cesarean section have been done in these cases, from clinical experience there is no evidence that they were indicated on reasonable grounds.

No authentic instances of transmission of the virus of poliomyelitis from the mother to the offspring in utero are on record. Unlike the virus of vaccinia encephalitis, measles, chickenpox and variola, which may be found in the bloodstream, the virus of poliomyelitis is rarely recoverable from the circulating blood of patients, or at any rate is never present in sufficient amount to pass through the placental circulation.

cannot be determined with any finality when we take into consideration that viruses with different characteristics make their appearance during one epidemic and in various parts of the country. The variations from year to year and variations in virulence of the virus are only a few considerations to be kept in mind in a critical evaluation of this matter.

One case of hematomyelia is cited which clinically simulated poliomyelitis.

ACUTE ANTERIOR POLIOMYELITIS COMPLICATING PREGNANCY

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Lancet 2: 353–355, September, 1947

A case is described in which acute anterior poliomyelitis occurred in the 6th month of pregnancy. The patient was treated conservatively and allowed to proceed to full term; a normal healthy female child weighing 9 lb. 4 oz. was successfully delivered. No complications occurred, except that there was delay at the pelvic floor and the child was delivered with forceps. Pregnancy and labor had no adverse effect on the gradual progress of the patient towards recovery of power; nor did the disease affect the expulsive power of the uterine muscle.

These findings are in accordance with American experience in similar cases. There is no evidence that the fetus can be infected before delivery. The only cases on record in which fetal death took place before delivery have been due to asphyxiation secondary to respiratory paralysis in the mother.

There is evidence that the newborn child has antibodies which protect it from infection in the first few weeks of life. A few cases of poliomyelitis in the first month are, however, on record.

On these grounds there is no evidence that interference with pregnancy or cesarean section is ever indicated in cases of poliomyelitis in pregnant women, except for circumstances which would equally apply to all pregnant women.

Aycock (New Engl. J. Med., 225: 405, 1941) estimated the probability of poliomyelitis and pregnancy coinciding at less than 1 in 1000 cases of poliomyelitis and less than 1 in 50,000 pregnancies.

Susceptibility in Pregnancy. The idea that the hormonal changes of pregnancy make women particularly susceptible to the virus is supported by animal experiment. (Jungeblut and Engle: J. Exp. Med., 59: 43, 1934; Aycock: Amer. J. Publ. Hlth., 27: 575, 1937; Endocrinology, 27: 49, 1940.) Aycock (1937) showed that injection of estrogenic substances into castrated immature female monkeys enhanced their resistance to intranasal instillation of virus. Comparative urinary estrogen assays showed higher excretion of these substances in poliomyelitis patients than in controls.

Weaver and Steiner (Am. J. Obst. & Gynec., 47: 495, 1944), among others,

done. As the appendix was congested, thickened and rigid, it also was removed. The left adnexa were left in place. Recovery of the patient was uneventful. The difficulty in diagnosis of this case is attributed to several factors. Endometriosis was not suspected because of the menstrual history (normal, regular, painless periods) and the existence of a pregnancy. Ruptures of chocolate cysts have been known to create peritoneal symptoms at the menstrual period and in 1945 Roux and Danion reported a case of tubo-ovarian endometriosis 10 days after a period and following rupture of a cyst, the size of an orange, adhering to a fibromatous uterus. Factors, such as chemical changes within the cyst and pressure of the enlarging uterus upon it, are discussed as possible causes of the rupture of the cyst, but it was impossible to arrive at definite conclusions. Menstrual symptoms were excluded because of the 5-month pregnancy.

(This case is very similar to one which occurred in our Clinic a few years ago and which was reported by Roger B. Scott: Am. Jour. Obst. & Gynec., 47: 608, 1944. The clinical picture was that of an acute abdomen and 3 possible diagnoses were entertained: (1) Twisted ovarian cyst; (2) acute appendicitis, and (3) degenerated myoma. Laparotomy was performed and immediately upon opening the peritoneal cavity, a moderate amount of brown, grumous material was encountered alongside the 34-week pregnant uterus. This came from a ruptured endometrial cyst which had become densely attached to the posterior uterine surface. As Burger points out, rupture of an endometrial cyst during pregnancy is an extremely rare complication and Scott, in his exhaustive review of the literature, was unable to find a single example of this condition.—Ed.)

THIOURACIL IN THE TREATMENT OF HYPERTHYROIDISM COMPLICATING PREGNANCY AND ITS EFFECTS ON THE FETUS

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Hyperthryoidism is a relatively infrequent complication of pregnancy. A severe hyperthyroid pregnant white female in the 26th week of gestation, presenting the classical clinical and laboratory findings characteristic of Graves disease, was treated with thiouracil up to and through the puerperium. Under thiouracil therapy .4 gram per day given in divided doses plus general supportive measures, she was symptom free at the time of her delivery. Her BMR, which had been +65 previously, had fallen within normal range as had pulse, blood chemistry and circulation time. An anencephalic monster was delivered which died 6 hours postpartum. Autopsy revealed a thyroid gland both microscopically and histologically normal, with weight and iodine content well within normal limits.

ACUTE MANIFESTATION OF ENDOMETRIOSIS DURING PREGNANCY

P. BURGER

The very rare occurrence of rupture of a chocolate cyst during pregnancy is reported. The patient was 34 years old, had had a child in 1935, adnexitis in 1942, and regular and painless menses until September 11th, 1945. During the night of February 12th, 1946, she was suddenly awakened by an extremely sharp pain in the lower abdominal region. At first these pains were felt on the right side but later become localized in the lower left quadrant. Vomiting followed the attacks. A diarrhea which had existed the evening before stopped and since the appearance of the pain more stools and gas were formed. At 8:00 A.M. the patient arrived at the clinic of the Maternité at Strasbourg. Her face was rather red and drawn with pain. However, her pulse was regular (92), her tongue wet, axillary temperature 37.6°C., and there was no appearance of jaundice. Examination of the abdomen by palpation was difficult due to the obesity of the patient and flinching from pain. The abdomen appeared very much swollen (in addition to obesity) and was completely silent. At gynecological exploration the external genitalia were cyanotic but there was no destruction. The cervix was in the axis, closed and soft. The uterus appeared large, near the end of the fifth month. It was pushed a little to the right and was painful at palpation. At the left there appeared to be an indefinitely outlined soft mass, about at the level of the base of the uterus, but this could not be determined exactly because of the severe pain. Severe peritonism was present, but the general appearance of the patient and the regularity of her pulse, precluded a diagnosis of peritonitis due to inflammation or toxicity due to perforated appendix. A temporary diagnosis of torsion of a cyst or twisted adnexa was made.

When the patient's condition had not improved by 4:00 P.M., intervention was decided upon. On opening the peritoneum a turbid fluid was found on the omentum which covered the lower part of the abdomen. The uterus presented the normal appearance of a 5-month pregnancy. The Douglas's pouch was filled with a great amount of turbid, viscous, brownish-black fluid (contents of a chocolate cyst). This fluid was sponged up and the peritoneum of the pouch seemed to be almost completely saturated with a blackish color. The left adnexa were congested and slightly amyloid but the tube appeared normal except for some thickening. The right ovary and tube were curled up, thickened, amyloid and very much contracted at the mouth. Together they formed an adnexal tumor the size of an egg, definitely endometrious and strongly attached to the lateral wall of the uterus. Disengagement of the right adnexa was difficult because of their intimate adherence to both the large ligament and the uterine wall. After their removal the surface of the uterine wall bled severely for an extent of 8 to 10 cm. As it became impossible to stop the hemorrhage by means of U ligatures and constrictions, a subtotal removal of the uterus was

Microscopically, the arteries and most of the arterioles of the lungs were occluded by a mixture of polymorphonuclear leucocytes, monocytes, acidophilic granular debris, and basophilic fibrillar material, and contained few or no red blood cells. Epithelial squamae and occasional bits of bile-stained granular debris were present in a few small vessels. The alveolar spaces were empty except for a few which contained a small amount of fluid. The bronchi were normal.

CASE 2

The patient was a 42 year old white tertipara who went into labor at term. Because of the excessive uterine distention, an abdominal binder was applied, the membranes were ruptured artificially and about 1 liter of amniotic fluid was drained off. During the following 4 hours little progress was made and 6 pitocin injections were given, 1 minim and 2 minim doses, alternating every half hour. This was ineffective and labor advanced slowly during the next 24 hours despite a repetition of the pitocin injections. Thirty-four hours after admission she began to have severe tetanoid contractions and made rapid progress. Two hours later the cervix was fully dilated and effaced. Fetal heart sounds were of good quality at this time. One hour later, the patient was delivered of a stillborn male infant by outlet forceps under nitrous oxide-oxygen-ether anesthesia. Immediately following delivery the patient became cyanotic, clammy and pulseless and died 65 minutes after the onset of symptoms despite immediate anti-shock treatment.

Autopsy was performed 2½ hours after death. On opening the abdomen about 200 cc. of bloody fluid were encountered. There was diffuse bloody extravasation into the preperitoneal tissues of the anterior abdominal wall below the umbilicus. There was also ecchymosis at the root of the mesentery and the mesenteric attachment of the terminal ileum and appendix, extending laterally to the cecum. This ecchymosis also involved the right broad ligament of the uterus with the corresponding tube and ovary. All these tissues were edematous. The blood within the heart and vessels was everywhere fluid; no clots were observed. Blood removed from the right auricle was incoagulable. It was placed in a refrigerator but unfortunately was not examined until 2 weeks later. After centrifugation, the sediment contained, in addition to the usual red cell layer and leucocytic cream, a top stratum of white flocculent material. Although shreds suggestive of mucus were found in smears made of this top layer, identification was not positive and the results were considered equivocal. The left and right lungs weighed 175 and 210 grams respectively and were grossly normal. The liver was normal except for severe pallor. There was moderate dilatation of the left ureter and the left renal pelvis. The uterus was normal for its puerperal state. The placenta was not available for examination. Other organs were normal.

Microscopically most of the pulmonary arterioles and alveolar capillaries were bloodless, and were occluded by polymorphonuclear leucocytes and a small amount of granular debris. Some of the larger vessels were similarly involved. Mucus as seen in Case 1 was demonstrable in a medium-sized artery, but no squamae were seen.

PATHOLOGY OF LABOR AND PUERPERIUM

PULMONARY EMBOLISM BY AMNIOTIC FLUID: REPORT OF 3 CASES WITH A NEW DIAGNOSTIC PROCEDURE

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The authors report 3 new cases of pulmonary embolism by amniotic fluid and also a procedure whereby the diagnosis can either be verified at autopsy or perhaps established when autopsy is impossible.

CASE 1

The patient was a 25 year old white secundipara. Twenty-one days after the expected date of confinement and 11 hours prior to hospital admission, bloody vaginal discharge appeared followed in 2 hours by labor pains. On admission uterine contractions were tetanoid in character, occurring at 5 minute intervals and lasting 20 seconds. Rectal examination revealed 3.5 centimeters' dilatation of the cervix with moderate effacement. The fetus was in the left occipitoanterior position of a vertex presentation and had a heart rate of 130 per minute. No significant abnormalities were found on routine physical examination. The blood pressure was 118/76. Temperature, pulse, and respiratory rate were within normal limits. The results of urinalysis and serologic tests were negative.

One hour after admission the patient was given demerol, 100 milligrams and scopolamine, grains 1/150 (0.4 mgm.) hypodermically. One hour and 45 minutes later the cervix was fully dilated and effaced. There was an emesis of undigested food particles at this time. Immediately after being placed upon the delivery table the patient became restless and complained of "chilliness." The skin was cold and clammy. This was followed by severe hyperpnea and coma. Within 15 minutes the patient was apneic, pulseless, and intensely cyanotic. There was conjugate deviation of the eyes to the right. The blood pressure was 30/00. Emergency measures evoked no response and death occurred 40 minutes after the onset of symptoms. A dead, cyanotic fetus was delivered during the last 5 minutes by version and extraction.

The autopsy, performed 2 hours after death, yielded only nugatory gross findings. However, the blood within the heart and vessels was everywhere fluid. No clots were observed. The left and right lungs weighed 225 and 270 grams respectively. There was a small amount of frothy, blood-tinged mucus in the left bronchial tree. The uterus was normal for its puerperal state. The placenta was not available for examination. The other organs were grossly normal.

Although the above findings were present throughout both lungs, they were not uniformly distributed. Nevertheless, there was very little blood in the pulmonary vascular tree. There was no pulmonary edema. The alveolar spaces and bronchi were empty but in some sections slight atelectasis was present. In the uterus a very significant lesion was found. A large blood sinus near the endometrial surface contained large masses of epithelial squamae.

The blood aspirated at the beginning of the autopsy did not coagulate. After centrifugation, done within 3 hours after death, the sediment showed 3 distinct zones instead of the normal 2. There was a broad, more flocculent zone of lighter color above the thin gray layer of leucocytic cream.

Smears were made of the top layer of sedimented material after the supernatant fluid had been removed. These smears were air-dried and stained with Wright's stain and with mucicarmine. The latter stain requires alcohol-fixation. The flocculent top layer was then transferred to a small tube and compressed by centrifugation. A portion was fixed in alcohol and the remainder in formaldehyde, and each was embedded in paraffin. The fixed middle, or leucocytic layer was similarly embedded. Sections were cut and stained with hematoxylin and eosin. Those from the alcohol-fixed block were also stained with mucicarmine and phosphotungstic acid-hematoxylin.

Both smears and sections showed the bulk of the upper flocculent layer to be composed of finely granular acidophilic material containing widely scattered small clusters of leucocytes. The smears also showed occasional single, long chains or rows of 10 to 20 leucocytes. In one smear of the top, flocculent layer of blood from the inferior vena cava, an occasional elongated mass of mucus was found. The mucus is characterized by its transparent, veil-like nature showing very fine, long, parallel fibrils all of which stained pink with mucicarmine. There were many eosinophils in and about the masses of mucus.

In the sections of the alcohol-fixed blood sediment, which were stained with hematoxylin and eosin there were small clumps of fine and coarse granules of golden yellow (bile!) color. Thin, wavy fragments, characteristic of squamae, were found in the sections but not in the smears.

(The concept of pulmonary embolism from the particulate matter of the amniotic fluid is one of the new few ideas which have been introduced into obstetrics during recent years. In their original paper on the subject Steiner and Lushbaugh documented this thesis with a mass of evidence which can leave little doubt that such emboli are not infrequently found in women dying suddenly in labor. (J. A. M. A., 117: 1245 and 1340, 1941.) However, the relationship between these emboli and the clinical pictures attributed to them is perhaps not as clear-cut, to most of us at least, as we should like to have it.

For instance, in the above paper by Gross and Benz, failure of the blood to coagulate is stressed as an especially characteristic finding in their 3 cases of amniotic fluid emboli. In the original paper by Steiner and Lushbaugh, as well as in their subsequent report (Am. J. Obst. & Gynec., 43: 833, 1942) this finding is not mentioned but quite other signs and symptoms are emphasized, notably, dyspnea, cyanosis, pulmonary edema, shock and uterine relaxation with postpartum hemorrhage. How can these emboli cause such a wide variety of disturbances?

Another question sometimes asked is why these amniotic fluid emboli rarely cause pain. In none of the 14 reported cases which have come to my attention, is chest pain mentioned.

CASE 3

The patient was a 35 year old white quintipara who went into active labor about 1 month prior to the expected date of confinement. All findings were normal. The patient was given demerol, 100 milligrams, and labor proceeded uneventfully for 6 hours. At the end of this time the cervix was fully dilated and effaced and the head was at the level of the ischial spines. The membranes ruptured spontaneously. It was noted at this time that the amniotic fluid contained fresh blood. Fifteen minutes later the delivery of a normal, live infant occurred spontaneously. The third stage lasted 4 minutes and was uneventful. Pituitrin, 1 cc., was given after the second stage and ergotrate, grains 1/320, (0.2 mgm.) after delivery of the placenta. No anesthetic was administered. For 20 minutes following delivery, the patient was alert and communicative. Then there was an emesis of green-tinted fluid. This was followed 5 minutes later by stupor, severe hyperpnea, and coldness and clamminess of the skin. The blood pressure was 40/20. The patient became comatose and pulseless within 15 minutes and respirations were slow and irregular.

At this time about 500 cc. of bloody fluid were expressed from the uterus and it was believed that shock had occurred from uterine hemorrhage. However, blood removed by venipuncture 25 minutes before death had a hemoglobin content of 10.8 grams per 100 cc. The plasma protein content was 5.8 grams per 100 cc. and the hematocrit was 32 by the copper sulfate specific gravity method. Death occurred 1 hour after the onset of symptoms despite antishock treatment.

Autopsy was performed about 1 hour after death. Immediately following the primary incisions and exposure of the abdominal and pleural cavities blood samples were aspirated from the inferior vena cava and from the pulmonary artery. A clean, sterile syringe with a No. 18 gauge needle and clean, sterile specimen bottles with rubber stoppers were used for this purpose.

After autopsy, it was felt that death could not be explained on the basis of the gross findings. The uterus was normal for its puerperal state. The placenta and membranes showed no abnormality. There was extensive thrombosis of veins of the broad ligaments. These thrombi were soft, of currant jelly type, and not attached to the vessel wall. Elsewhere the blood was thin and fluid and no clots were found.

Microscopically, in the lungs, there were extensive vascular occlusions beginning with the medium-sized pulmonary arteries and extending down to the alveolar capillaries. The lumina of these vessels were filled with a mixture of loosely packed leucocytes and acidophilic granular material. Longitudinally-cut hair shafts (lanugo) were found in 2 of the larger arteries. This hair was demonstrable in 7 consecutive serial sections of one of these vessels. In 2 smaller arteries the leucocytes appeared to be "combed-out" in parallel rows or lines containing in addition, fine acidophilic granules and a few epithelial squamae. This "combed-out" appearance of the leucocytes and granules was characteristic of mucus within the vessel. No fat was demonstrable in frozen sections stained with sudan IV.

injected with doses ranging from 0.000,045 to 0.000,067 gram per gram of body weight. All the animals responded with definite and unmistakable symptoms almost immediately after injection. These consisted of restlessness, tremors, marked dyspnea and convulsions. The 3 guinea pigs that were injected with the smaller doses recovered but the one that was injected with the highest dose died two minutes after injection. Marked congestion, hemorrhages, embolism and thrombosis were common in the lungs of all. With the highest dosage of the charcoal the blood had not coagulated at the end of 32 minutes after death. The results from the intravenous injection of Fuller's earth were similar to those from the injection of charcoal but the severity of the symptoms was greater and coagulation of the blood was more completely prevented. In fact, coagulation of the blood did not occur in any of the 3 guinea pigs injected; all died within a half hour. The authors believe that these differences may depend upon the differences in fineness or dispersion of the particles, which were smaller in the case of Fuller's earth than of charcoal. Comparable results were obtained with India ink, the animals showing marked dyspnea with death at the end of 3½ minutes, coagulation of the blood being considerably retarded. Opaque masses or spicules of India ink were found in the veins, arteries and capillaries of the lungs.

Hanzlik and Karsner interpret their studies as indicating that a large number of chemically and physically unrelated agents, when injected intravenously, produce similar symptomatic and histologic changes. They also produce definite chemical and physical changes in the blood. All this indicates the operation of a common, fundamental cause, or causes, in the development of these phenomena. They regard their findings as being in somewhat the same vein as certain previously reported work in which the role of *pulmonary blockage* was emphasized as being responsible for many of the systemic changes.

When the above observations on anaphylactoid shock are considered, together with Steiner and Lushbaugh's original statement that amniotic fluid emboli act in just this same manner, some of the confusion that has existed concerning these emboli may be cleared. The mechanism to be pictured is quite similar to that which happens when a minute amount of a suspension of Fuller's earth is injected into an animal,—the especial point to be noted here being that the particles are extremely small. In this connection it will be recalled that the lungs in the 3 cases of amniotic fluid emboli reported above by Gross and Benz were normal on gross examination (no emboli or infarcts) and only on microscopic examination were they found. It is this extremely minute size of the particles, with their large surface area which, in the opinion of Hanzlik and Karsner, is responsible for their ability to produce various blood chemical changes such as lessened coagulability of the blood. The small size of amniotic fluid emboli would appear also to be the reason why they seldom cause pain.

From what has been said it is evident that anaphylactoid shock, with its common denominator—pulmonary blockage—may produce such a wide variety of grave signs and symptoms experimentally as to make it quite plausible that many of the various phenomena associated with amniotic fluid emboli, including lessened coagulability of the blood, may well be attributed to it. Certainly, the case above of Gross and Benz, in which there were 200 cc. of blood in the peritoneal cavity, with widespread extravasation of blood, fits satisfactorily into the picture. But whether it can produce postpartum hemorrhage through the medium of shock, as Steiner and Lushbaugh claim, I am not so sure. As the latter authors point out, in their 2 cases of rupture of the uterus, the amniotic fluid emboli may have been sub-clinical in degree and in any event were not the main cause of death.

All in all, this conception that amniotic fluid emboli may cause anaphylactoid reactions and thereby sudden death in labor, is a most intriguing theory with much evidence to support it, both experimental and clinical. The report of additional clear-cut cases is needed, however, before it can be regarded as completely documented. Meanwhile, let us be careful not to make it a waste-basket for all cases of unexplained death in labor, especially cases without autopsy confirmation. This will serve only to obscure the issue and abuse a fine concept.—Ed.)

Indeed, in the case of Hemming's (long a student of embolism) the clinical diagnosis of pulmonary embolism was ruled out because of the absence of this classical symptom of thrombotic embolism, yet at autopsy amniotic fluid emboli were found.   (Am. J. Obst. & Gynec., 53: 303, 1947.)

Moreover, why is it that amniotic fluid emboli are so frequently associated with grave abnormalities of uterine behavior which, themselves, are known to be common causes of sudden death during or soon after labor?   In the original 8 cases reported by Steiner and Lushbaugh, the uterus was packed in 5 because of postpartum hemorrhage due to uterine atony, while in a 6th there was outright rupture of the uterus.   In their 2 cases reported subsequently, 1 showed at necropsy a 3 cm. rupture through the left posterior uterine isthmus with "about 4000 cc. of bloody fluid and dark bloody clots in the peritoneal cavity." In the other of these 2 cases the patient died from shock shortly after a laparotrachelotomy done for central placenta previa.   In the second case reported by Gross and Benz, as noted in the above abstract, 200 cc. of bloody fluid was found at autopsy in the abdominal cavity with widespread extravasation of blood under the pelvic peritoneum; no rupture of the uterus, however, was demonstrable.   In other words, in 8 of the 14 cases of amniotic fluid emboli under consideration, local pelvic conditions were present which themselves might conceivably have been the cause of death rather than the emboli.

In talking to obstetricians here and there, I gather that the above circumstances have given rise to some little confusion about this whole pathological entity and even some skepticism about its validity as a cause of death.   As I see it, a good part of this confusion is due to a misunderstanding of what Steiner and Lushbaugh originally set forth as the underlying mechanism at work in this condition.   The misunderstanding has been abetted by a tendency to associate amniotic fluid pulmonary embolism with thrombotic pulmonary embolism, a quite different condition in many respects.   Steiner and Lushbaugh made their opinion quite clear, namely, that the phenomena which follow in the train of amniotic fluid emboli are due to *anaphylactoid shock* from the sudden deposition of the amniotic material in the pulmonary arterioles.   This anaphylactoid reaction in turn causes the vascular collapse and this in turn the postpartum atony and hemorrhage.   In the opinion of Gross and Benz, this same anaphylactoid reaction may be held responsible for the incoagulability of the blood present in their cases, with extravasations beneath the peritoneum, as well as for various other forms of purpura.

Our problem then resolves itself into the question: Can anaphylactoid shock produce the many different phenomena mentioned above and if so, how?

Perhaps the most convincing, as well as authoritative, answer to this question can be had from the pioneer studies on anaphylactoid shock carried out in the early twenties by Paul J. Hanzlik, Department of Pharmacology, Stanford University, and Howard T. Karsner, now Professor of Pathology, Western Reserve University.   (J. Pharmacol. & Exper. Therap., 14: 379, 425, 449, 463 and 479, 1920; Ibid, 23: 173–235, 1924.)   In their earliest studies it was shown that the intravenous injection of a variety of agents in untreated guinea pigs caused systemic reactions which the authors characterized as anaphylactoid reactions.   The symptoms from many of the agents were found to be indistinguishable from those of anaphylactic shock, but the lungs showed important differences, grossly and histologically, from those of anaphylactic shock.   These differences consisted of pulmonary congestion and hemorrhages together with *thrombosis and embolism which were present in the lungs of the animals injected* with the different agents, but were absent in true shock.   The entire study of Hanzlik and Karsner comprised an investigation of the symptoms, histologic changes in the lungs and effects on the coagulation time of blood from a total of 71 different agents injected intravenously in 365 guinea pigs, 4 cats and 2 dogs.

In the belief that embolism and thrombosis were responsible for the pulmonary changes and symptoms produced by the various agents injected, Hanzlik and Karsner reasoned that similar effects should be promptly reproducible, in part at least, by the injection of a suspension of charcoal particles.   This was found to be the case in the 4 guinea-pigs that were

out haste or force, and the fetal heart should be auscultated frequently. Using the tips of the fingers, one raises the breech gradually from the pelvis and attempts to carry it up to the side on which the back is found. Usually the fetus turns best in flexion as if making a somersault, but if it will not turn in one direction the opposite should be tried. After the breech has been raised and the baby rotated almost into a transverse position, light pressure on the head in the opposite direction will cause it to slip easily into position over the pelvis brim. No anesthesia should be used. If the first attempt is unsuccessful, it should be repeated at other visits. If accomplished, the position should be checked at each visit. X-ray may help in showing location and placement of extremities.

Objections may be raised that version is hard to perform, that it coils the cord about the infant's neck, that it may cause separation of the placenta, premature labor, etc. In Ryder's series of 1700 cases, however, the incidence of premature labor was less in those who had external version than in those who did not, and there was no instance of premature separation. On the other hand, the advantages are considerable: The presentation may be changed to one far safer, usually with a shorter and more comfortable labor. Disproportion between head and pelvis can be recognized. Premature labors are less likely to occur. The patients are frequently much more comfortable.

In estimating the prognosis for a patient with a breech presentation, every method of investigation should be used. Seasoned judgment and experience are of greatest value.

While breech presentation in a primipara is not of itself an indication for abdominal delivery, elective or early cesarean section offers the best hope of lowering the fetal mortality in breech cases complicated by a moderate disproportion. In doubtful cases the patient may be allowed to go into labor under close observation. If dilatation of the cervix is rapid and unimpeded, the possibility of vaginal delivery of the aftercoming head must be decided. When contractions are of poor quality and dilatation and descent are slow, or in presence of such factors as a history of stillbirths, sterility, or advanced age, cesarean section must be considered.

The author presents four case reports to illustrate some of these difficulties which may appear in breech management.

METHOD OF TREATING MASSIVE OBSTETRIC HEMORRHAGE

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Preliminary Typing of Blood. For over 3 years it has been the practice of the Woman's Clinic of the New York Hospital to determine the blood group and

MANAGEMENT OF BREECH PRESENTATION

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The author, like other writers such as Potter and Dieckmann, believes that breech delivery presents the practitioner with more real difficulty than any other single problem.   In uncomplicated breech deliveries the fetal mortality is probably 3.5–4 per cent for term pregnancies.   Greater risks of injury and hemorrhage are involved for the mother.

Usually such cases are given special attention.   They should be thoroughly studied, both clinically and roentgenologically, before labor commences.   Abdominal delivery should be considered in the elderly primipara, especially if there is any cephalo-pelvic disproportion and if x-ray has eliminated the presence of gross deformity of the fetus.

In management of vaginal delivery in breech presentation, methods range from the conservative, where assistance may be rendered only when it is found that the patient is unable to deliver herself, to a preference for breech extraction under surgical anesthesia as soon as complete cervical dilatation is reached. The author believes that the latter procedure should be restricted to those specially trained in the technic.   Tentorial tears, cerebral hemorrhage, intracranial damage and asphyxia are the most common causes of infant mortality, and cord injuries are not rare.   Potter stresses the difference of breech extraction from extraction with version in that the arms are most apt to become extended, the head is extended, and the head is unmolded.   Furthermore, the inexperienced operator may mistakenly attempt immediate delivery, rather than allowing the patient to deliver herself until the umbilicus is born and then giving assistance. The author stresses that episiotomy, in all cases unless the perineum is very greatly relaxed, and application of forceps to the after-coming head, whenever any real difficulty is found in its delivery, may be life-saving.   Use of the forceps is not hard and is far less dangerous than the obsolete Mauriceau maneuver.

Because of the risks involved in breech delivery, the performance of external cephalic version to convert to vertex presentations is often recommended.   The author knows of no case where an accident has occurred to either mother or baby from this method.   The maneuver has not become popular apparently because the breech presentation is not recognized early enough, and because the procedure is not done often enough for acquisition of skill.

The earlier in pregnancy, the easier is the version.   The thirty-second to the thirty-fourth week is generally considered the optimum time.   This of course requires a routine check-up and a definite diagnosis of presentation at this time. Although some will undergo spontaneous version, this should not prevent the attempt at rotation.

In performing an external version the patient, completely relaxed, is placed upon her back on the table.   Manipulation should be cautious and gentle, with-

A Method of Rapid Transfusion

When a patient is suffering shock from massive blood loss, the ordinary drip method of blood transfusion is wholly unsuitable. Studies here indicate that if recovery is to occur, at least 40 per cent of the total blood lost should be replaced during the first hour following the initial hemorrhage. Rapid treatment should not be stopped until there has been a definite response in the blood pressure, and thereafter blood may be given by the usual methods until there has been 100 per cent or more replacement. When an exceedingly large volume of blood has been lost, such rapid replacement is not possible by the drip method. Consequently, during the past 3 years, a simple pressure mechanism has been added to the ordinary transfusion apparatus (Fig. 1).

Using this apparatus and maintaining a pressure of 120 mm. of mercury in the bottle of citrated blood, 500 cc. of blood may be given quite rapidly (in 7 to 10 minutes using an 18 gage needle, in 2 to 5 minutes using a 15 gage needle). Veins of the arm or hand are usually selected as the site for transfusion. Saphenous and femoral veins, although of better caliber, are usually not readily available during obstetric procedures.

Alkali Agents

Dextrose and isotonic solutions of sodium chloride have been all but discarded as therapeutic measures; instead, sixth-molar sodium lactate solution is now used. It has long been known that a straight line relationship exists between the fall in blood pressure and the alkali reserve. Experimental evidence discloses that if the acidosis of shock is not combated it may be a major factor in so-called irreversible shock by featuring in myocardial and capillary damage. By definition, recovery from irreversible shock is impossible; but there is evidence that the administration of alkali agents proves useful in delaying the onset of irreversible shock until the more effective agents, such as blood and plasma, are available in sufficient quantity. The secondary purpose in giving alkali agents is to combat transfusion reactions which might presumably occur when multiple transfusions are administered.

The previously described methods have been used on both the obstetric and gynecologic services. Since the method was adopted there have been no deaths from hemorrhage during 3,600 major and 3,900 minor gynecologic operations. On the obstetric service 1 death due to hemorrhage occurred during 14,000 deliveries.

(This practical and instructive article may well be heeded by obstetric departments everywhere because it sets forth concisely and logically the steps which must be taken if gravidae are to be completely protected against hemorrhage. In a dramatic case of abdominal pregnancy which was recently managed by the Department of Obstetrics in nearby Sinai Hospital in Baltimore, the stupendous amount of 8000 cc. of blood was given the patient within 4 hours. She survived, but only because she was given this massive amount of blood rapidly. The emphasis which Cole lays on the importance of rapid transfusion in cases of exsanguination is therefore completely justified, but there are ways other than the apparatus pictured by which the same end may be achieved. Perhaps the simplest (pro-

the Rh type of all patients at their first antepartum visit. In an earlier publication the value of this procedure was indicated and the author now wishes to emphasize it again. In massive hemorrhage, as will be shown, the time factor is of great importance, and any measure directed toward obviating delay in transfusion should not be overlooked.

Precautionary Measures

It has been the policy in this hospital to crossmatch the blood of all patients prior to delivery if it appears that a large loss of blood may occur. Thus, in cases of twins, hydramnios, myoma uteri, varicosities of the vulva, excessive size of the infant, manual removal of the placenta, or when a difficult forceps delivery is anticipated, the blood of the patient will have been crossmatched during labor, and 1 or more pints of blood will be held on call for immediate use at the central blood bank. In the case of cesarean section it has long been a clinic rule that the operation is not to commence until 1 pint (473 cc.) of suitable blood is present in the operating room. Recently precaution has gone one step further. The intravenous administration of sixth-molar sodium lactate solution is started at the time of operation, using a recipient transfusion set and a needle of adequate caliber. Thus, if a transfusion is needed during the cesarean section, a search for veins will not be necessary.

The Time Factor

In the treatment of hemorrhagic shock delay in initiating appropriate therapy is hazardous. Many times it is a fatal error. The delay may usually be traced to ineffectual methods of transfusion, optimistic estimates of the amount of blood lost and hopeful waiting for the patient herself to overcome irreparable blood loss. Again, the surgeon who overlooks a primary hemorrhage resulting in hemorrhagic hypotension may suddenly be faced with a secondary hemorrhage and irreversible shock. It has often been observed that the longer a patient is in a state of shock the more difficult treatment is and the more unfavorable the prognosis.

The Obstetric Blood Bank

It seems almost unnecessary to state that the development of blood banks has done much to reduce the number of hemorrhagic fatalities. The New York Hospital has been fortunate in having a large, active, general blood bank. In spite of these facilities it has been found most useful to have a small obstetric blood bank on the delivery floor itself. This bank contains 2 pints (946 cc.) of type O, Rh negative, citrated whole blood which has been treated with Witebsky blood group specific substance to eliminate anti-A and anti-B factors. Two pints (946 cc.) of commercial dried plasma are also held in reserve. This blood may be used for any patient without preliminary typing or crossmatching and is replaced from time to time as it ages. Any unit removed from this bank is used only in an emergency, and the unit must be immediately replaced.

apparatus was left with the blood running. The blood ran out, was followed by several hundred cc. of air and the patient died instantly.—Ed.)

CONCEALED RUPTURE OF THE UTERUS

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This is a detailed history of a 37 year old gravida 9 who entered the hospital December 14, 1945 near term because of labor pains. She was discharged after 24 hours as not in labor but returned shortly thereafter because of epigastric distress and a feeling of fire under her right breast which radiated to the right loin. Her temperature was 102.4; urine showed 2+ albumin with numerous free and clumped white cells. Pyelitis was diagnosed, penicillin and sulfadiazine given, and the patient discharged well on December 29, 1945.

She returned one month later having noticed little in the interim except the absence of fetal movements and a reduction in size of the abdomen. The general impression after examination was extrauterine pregnancy. X-rays revealed a dead child in the transverse position.

At cesarean section clear serum was found in the peritoneal cavity. The uterine surface was mottled green and purple. Omentum and bowel could be seen adherent to the uterus and emerging from the uterine cavity. After delivery of a macerated infant the placenta was found incorporated in the uterine wall. A subtotal hysterectomy was then done leaving the adherent portions of the uterus clinging to the bowel. With supportive therapy the patient made an uneventful recovery and was discharged on the sixth postpartum day.

In a review of this subject only one American report of concealed rupture was found from 1937 to 1945. However, silent uterine ruptures were found to be more common in European Clinics.

Two case reports of unrecognized spontaneous rupture, one by S. Blakely and another by Von Jaschke, are also given in detail.

POSTPARTUM HEMORRHAGE AND SHOCK

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The majority of maternal deaths are due to obstetric hemorrhage, puerperal infection and the toxemias. The chief causes of obstetric hemorrhage are extra-

vided the tubing is thick-walled enough to prevent its collapse) is to use a 3-way stop-cock, attach a 50 cc. syringe to the system and pump blood in with the syringe.
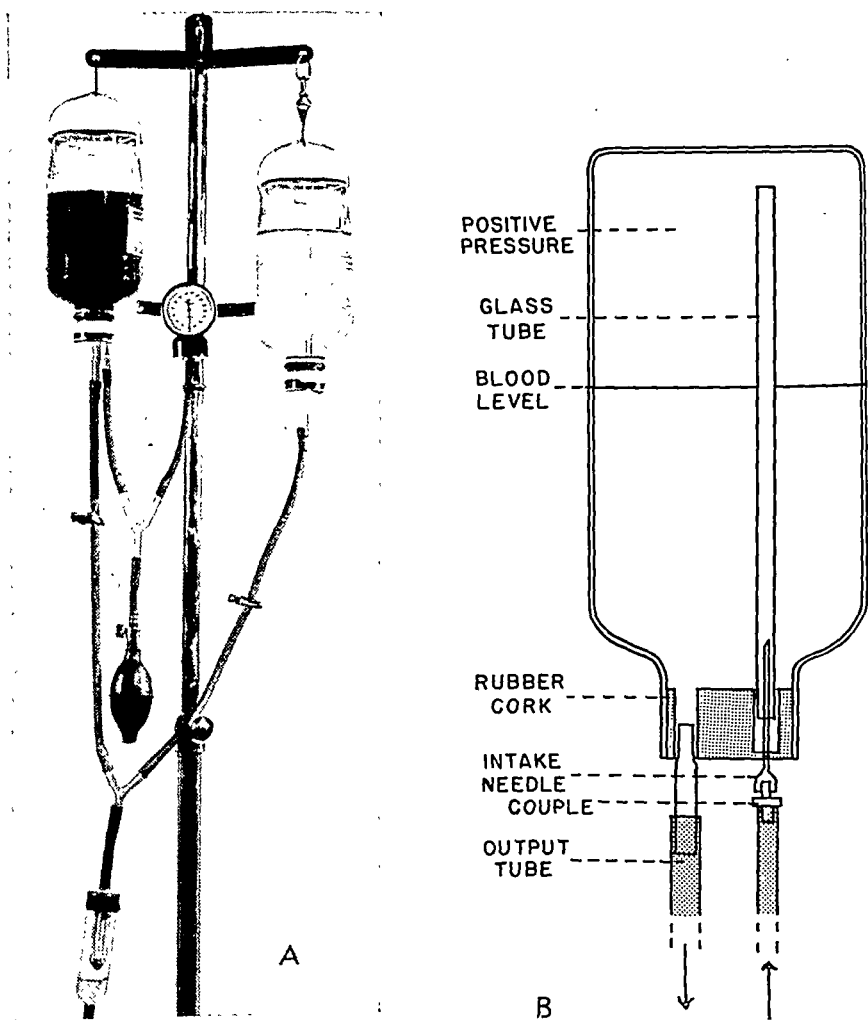
FIG. 1.   A, Photograph of standard, closed method transfusion set with simple pressure attachment in place.   The left flask contains blood; the right flask contains sixth-molar sodium lactate solution.   They are connected by the lower Y tube to a filter from which solutions pass to the patient.   The central Y tube connects a sphygmomanometer bulb, aneroid meter and the air-intake needle of the blood bottle.   The connection to the air-intake needle may be made by slipping the tubing over the needle or by employing the metal coupling from a sphygmomanometer.   The coupling makes an exact fit with a standard needle.   B, detailed sketch of pressure connection to the blood bottle.   (Courtesy of Dr. John T. Cole.)

The apparatus recommended by Cole and shown in Fig. 1 is doubtless satisfactory but a word of warning is in order: the eye of the physician must not be taken off it for an instant. I know of a case in which, after a head of pressure had been built up above the blood, the

stage of labor. With patients under analgesia, anesthesia, and on hospital beds, etc., one can no longer speak of normal deliveries. However, if one imitates the normal mechanism of labor, results will be markedly improved. For a proper separation of the placenta, it is of the utmost importance that the baby be delivered slowly—in stages with a thirty to sixty second pause after the delivery of each shoulder—requiring a total of at least three minutes. Thus the uterine wall is given time to contract and retract thereby tearing itself away from the placenta. The latter has usually separated within less than one minute. After the fetus has been expelled, and as soon as the uterus retains its globular form, it should be compressed but not pushed into the pelvis. When the placenta is in the vagina it should be extracted by pulling on the cord. The authors do not believe that an oxytocic is necessary for the separation of the placenta; but since patients are not under normal conditions—anesthesia, etc.— they believe that one unit of solution of posterior pituitary or 0.2 to 0.4 mg. ergotrate should be injected intravenously after the posterior shoulder if the doctor is experienced; if he is not, then after the delivery of the placenta. This will prevent excessive bleeding after the placenta. The authors' nurses give many of the intravenous injections. The authors believe that intravenous injections of pituitary are much more efficacious in producing uterine contractions than ergotrate, but the latter has a longer action.

If the placenta cannot be delivered and there is no bleeding, one may wait, at a maximum one hour, but all retained placentas should be manually removed at the end of this time. Nothing is gained by waiting hours for the separation of the placenta and the authors' resident staff is instructed, if there is no bleeding, to remove the placenta manually within one hour at a maximum and usually within 15 minutes after delivery.

Uterine hemorrhage is treated by the immediate removal of the placenta, manually if necessary, or after the third stage by manual palpation of the uterine cavity and visual inspection of the vagina and cervix. One of the above oxytocics should be injected intravenously and repeated one time. At the same time the uterus should be massaged briskly through the abdominal wall. If the bleeding continues, the uterus must be packed. A transfusion of 1,000 ml. or more of blood, if necessary, must be given at once. Periodic hemoglobin or hematocrit determinations must be made.

Studies of postpartum hemorrhage occurring after the tenth day are still being continued. During the last six months of 1946 there was one curettage because of hemorrhage two weeks postpartum. In preceding similar periods, the number has varied from five to twelve. Manual exploration of the uterus in these patients was given up many years ago because of the high mortality from infection. The uteri are curetted with a large dull curette. Only in rare instances has a piece of placental tissue been found. The usual finding is thrombosed vessels from the placental site. The authors think the delayed postpartum hemorrhage may be due to faulty involution of the placental site resulting from the ergotrate.

There have been several reports about the dangers of shock and death from injections of solution of posterior pituitary. In a rather long period of full-

uterine pregnancy, abortion, placenta previa, premature separation and post-partum hemorrhage, the last being responsible for the largest proportion of maternal deaths. The causes of postpartum hemorrhage are: (1) uterine inertia; (2) extensive lacerations of the birth canal; (3) retention of the placenta or parts of it in the uterus; and (4) less common conditions such as uterine rupture, vulvar varicosities, inversion of the uterus, and mismanagement of the third stage of labor.

The treatment of postpartum hemorrhage and shock is first of all prophylactic. A patient should have adequate prenatal examination and care. Also careful management of labor is important in that maternal exhaustion should be prevented or relieved by giving proper rest periods and intravenous fluids. Excessive analgesia and anesthesia should be avoided. During the third stage of labor the amount of bleeding and the state of the uterine fundus should be closely observed. The placenta should be inspected, oxytocic drugs given to accelerate and accentuate uterine contraction, and the patient watched for at least one hour after delivery.

In the management of postpartum hemorrhage the first consideration is to control the bleeding, the second is to replace the lost fluid; and the third to treat the shock and anemia.

If bleeding results from incomplete separation of the placenta of its incarceration in the uterus, delivery of the placenta is imperative. This may be done by simple expression or, if this fails, by the Credé maneuver, or manual removal if the latter fails. If bleeding continues after the placenta is out and oxytocic drugs have been given, bimanual massage of the uterus is employed. If bleeding persists the birth canal is inspected for lacerations and these are repaired. When bleeding continues after the above measures have been carried out, the uterus should be packed. Occasionally hysterectomy has been done for massive uterine hemorrhage, or bleeding caused by submucous fibroids. Hysterectomy is imperative in uterine rupture.

Fluid loss should be replaced immediately and in adequate amounts by properly typed, Rh'd and crossmatched whole blood. Intravenous glucose is always started at once followed by whole blood, plasma, or solutions such as acacia or gelatin, depending on their availability.

THE PLACENTAL STAGES AND POSTPARTUM HEMORRHAGE

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The prevention of postpartum hemorrhage is much easier than the treatment. Prevention begins with the proper conduct of the terminal phase of the second

sitions included 39 posterior, 41 breech, 3 face and 4 transverse. There were 3 sets of twins and 43 stillbirths; 100 were primipara, 86 para II, 32 para III, 16 IV, and 25 V or more. In 62 cases the placenta was adherent, in 92 retained; no note was made in 103. There were no cases of placenta accreta.

In a following controlled study of 234 personal cases, 150 routine or prophylactic manual removals of the placenta were done within 10 minutes following delivery, most within 4 minutes. There were no deaths. Morbidity occurred in 3 patients (2 days each), or 2 per cent; corrected morbidity was 1, or 0.66 per cent. Two were due to breast disturbances, the remaining one unexplained.

Delivery was spontaneous in 33, operative in 117: 75 by prophylactic, 33 low, 8 midforceps, and 1 high forceps. There were 42 posterior positions, 10 occiput transverse, 9 breech, and 2 face.

When an obstetrical patient is admitted and prepared for labor, the perineum is sprayed with a 2 per cent solution of mercurochrome and the vagina instilled with 2 drams of the same solution. This is repeated every 12 hours until the patient is ready for delivery. At this time the perineum is cleansed with soap and water and sprayed with a 2 per cent acetone alcohol solution of mercurochrome. The perineum is then depressed and 2 drams of a 2 per cent solution of mercurochrome in glycerine is poured into the vagina. By sweeping the fingers around the presenting part, the solution is brought into contact with the greater part of the vagina. When a manual removal is anticipated, this is repeated three times. (For a complete description see the previous publication, West. J. Surg., 51: 201–209, May, 1943.)

As soon as the baby is delivered, the perineum is cleansed of as much blood as possible, sprayed again with the acetone alcohol solution of mercurochrome, and the vagina instilled again with the mercurochrome in glycerine. Gloves unchanged, the hand is passed into the vagina and the placenta removed. At times the placenta is found in the vagina; not infrequently, the hand passes into the uterus but within the amniotic sac. Traction in the cord often makes the removal easier, but it may be necessary to puncture the placenta in order to get a sufficient grasp to do the removal. If the placenta adheres, the fingers are swept back and forth between the uterus and the placenta until it is separated. If delivery has been difficult and the placenta is broken up, the hand should be passed back into the uterus to make sure no fragments remain. If the cervix should close down before the removal, it may be necessary to break up the placenta to get it out, and again care should be taken to remove all fragments.

The patients were delivered under anesthesia, which was usually stopped following delivery; in an episiotomy, it was stopped until the obstetrician was ready to close the perineum, then resumed, removal of the placenta being done before the episiotomy. Deep anesthesia is not necessary for manual removal of the placenta. Many removals were done with the patient out of the anesthetic, and with frequently much less pain than when the placenta is expressed by pressure from above.

Three different types of treatment by oxytocics were given to 50 patients each. Group 1 received 10 units of pituitrin intramuscularly immediately after delivery

time obstetrics, the senior author has encountered one patient who is unusually sensitive to pituitary.   He has seen infrequent reactions from this drug but none fatal or alarming other than those due to rupture of the uterus from tetanic con- traction.   In the present study, over 2,000 patients have received one or two units of pituitary during the terminal portion of the second or third stage of labor, and there have been no recorded reactions attributable to the drug.,

(See editorial note which follows next abstract.)

MANUAL REMOVAL OF THE PLACENTA

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The author contends that early manual removal of the placenta, granted proper antisepsis, is indicated in the presence of an anticipated difficult third stage.   The hazard of infection can be overcome by routine vaginal antisepsis during labor and at delivery, and the blood loss, shock or trauma which may occur with the Credé maneuver or in the one or two hours' delay following delivery, may be prevented.

Although DeLee believed that if the operator actually knows and practices antiseptic technic, he can safely invade the postpartum uterus, many writers believe that the use of manual removal should be limited, and waiting for an hour or more before the attempt is advised.   In 1,157 manual removals (about 1 to 128 deliveries) reported in the literature there were 56 deaths, a mortality of 4.8 per cent.   Morbidity, where reported, ranged from 35 to 55 per cent.   About one-third of these cases were delivered before vaginal antisepsis was widely prac- ticed and before sulfa drugs and penicillin were available.

Records on manual removal of the placenta show favorable results from the vaginal antisepsis in labor and at delivery routinely used at Methodist Hospital for 22 years.   In 12½ years, in 22,264 vaginal deliveries there were 260 cases of manual removal of the placenta, or 1 in 85.9 deliveries.   There was only 1 death —a patient with a placenta previa admitted in critical condition after a physician had tried to deliver her at home died on the ninth day from a pulmonary embo- lus—a mortality of 0.4 per cent.   The morbidity was 10.8 per cent, corrected to 9.2 per cent, with the longest morbidity 15 days for a patient with parametritis who was in the hospital 36 days.

In most cases the Credé maneuver was tried repeatedly, and as it failed, manual removal was done, usually within 20–30 minutes.   One patient was given four units of plasma and a transfusion of 500 cc. of blood, and the placenta left in 2½ hours.   She had a rise in temperature of 100.2°F. for one day.

Deliveries were spontaneous in 151 of the 260 cases.   Of the remainder 88 were by low or prophylactic forceps, 12 by midforceps, and 9 by bag induction.   Po-

Manual removal of the placenta has definite advantages in preventing blood loss and in sparing the patient the Credé maneuver. The morbidity and mortality would be greatly reduced if manual removal were performed, under antiseptic technic, without delay when difficult third stage is anticipated. Manual removal of the placenta is not, however, recommended as a routine procedure. 3 tables.

(The paramount recommendation in the foregoing paper by Dieckmann and his associates—one which supersedes in Dieckmann's opinion the matter of oxytocic drugs—is slow, very slow delivery of the shoulders followed by slow extraction. As the tables which document this article attest, between the alternative of rapid extraction of the infant *with* oxytocics and slow delivery *without* oxytocics, the latter gives better results both in respect to duration of the third stage and blood loss. He finds, moreover, contrary to current notions, that oxytocics given at the end of the second stage make little difference in the time of placental separation, but do affect slightly the amount of blood lost with the placenta and very definitely the blood lost after placental delivery. The stress on slow delivery is sound teaching, commonly neglected, and deserves all the emphasis which the authors give it.

In regard to oxytocics it is instructive at this point to turn to the concluding paragraphs of the Mayes abstract, especially the last. Here it is reported that when oxytocics are given before delivery of the placenta, separation is more rapid but not decidedly so (2–3 minutes vs. 4–5 minutes). Certainly the differences noted by Mayes are not so great as to contradict sharply Dieckmann's contention that early oxytocics have no effect on placental separation. In regard to blood loss, Mayes' findings differ from Dieckmann's in showing little variation between the group in which pituitary extract and ergotrate were administered after the delivery of the placenta and the two groups in which they were given earlier; and surely, in this respect, his Group 1 and Group 2 are almost identical.

In sum, if these two papers are studied carefully, one after the other, the impression is received that they rather counterbalance one another in regard to the effect of early oxytocics and that the net yield of ergotrate with the posterior shoulder is almost nil in regard to expediting the third stage and somewhat equivocal in regard to reducing blood loss,— at least when compared with later intramuscular use.

Concerning intravenous pituitary extract with the birth of the anterior or posterior shoulder, here the question of safety arises. Dieckmann has been correct about so many things obstetrical that there is good reason for believing that he is also correct about the safety of this procedure. I certainly hope so, but question it. During the thirties we used intravenous pituitary extract quite frequently but gave it up because we did see, contrary to Dieckmann's experience, a number of cases of worrisome "pituitrin shock." Moreover, just recently, the following case has come to my attention: in one of our outstanding obstetrical clinics, a patient was being delivered by cesarean section under spinal anesthesia. Following delivery of the infant, when the mother was apparently in excellent condition, she was given approximately 2 units of pituitary extract intravenously and was dead within a few minutes. Of course, death may conceivably have been due to other causes, but it was the unproven opinion of those present that exitus was the result of the intravenous pituitary extract. Dieckmann himself refers to other such reports.

Having tried out ergotrate with the posterior shoulder back in 1940 and having watched the ups and downs of this procedure over the intervening years, I am inclined to feel that the routine which we have employed for the past decade is probably the safest for general use and just about as efficacious as any other, namely: 1 cc. of pituitary extract intramuscularly immediately after the birth of the infant followed by ergotrate 0.2 mg. intramuscularly immediately after the delivery of the placenta.—Ed.)

of the baby and 1/320 gr. of ergotrate intramuscularly immediately after delivery of the placenta. Usually two minutes after delivery of the baby the hand was passed into the vagina; the placenta was removed within 2 to 6 minutes, in one case not until 9 minutes. It was found in the vagina in 2 patients, in the cervix in 10, lower uterine segment in 14, and fundus in 18. Six had been delivered before note of location was made. Blood loss was 50 cc. or less in 34 patients, and frequently so small it could hardly be measured. Only 5 lost more than 100 cc. and in only one of these did blood loss reach 250 cc. None was transfused. Two patients were later readmitted for bleeding, both curetted and a remnant of placental tissue found in one, but with no morbidity in either. Only 2 in the group had a red cell count under $3\frac{1}{2}$ million and only 3 a hemoglobin less than 10 grams.

In group 2 patients were given 1/320 gr. of ergotrate intravenously as soon as the baby was delivered. The placentas, found in the cervix in 21, lower uterine segment in 20, and fundus in 9, were all removed in 2 to 5 minutes. Blood loss was 50 cc. or less in 33, and over 100 cc. in only 4, the largest amount being 250 cc. In 4 patients the red cell count was 3–$3\frac{1}{2}$ million, in 3, $3\frac{1}{2}$–4 million, and in 43, over 4 million. All but 3 had hemoglobin over 10 grams.

In the third group no oxytocics were given till after removal of the placenta, then 10 units of pituitrin intramuscularly and 1/320 gr. of ergotrate intramuscularly about 10 minutes later. It was found best here not to try to remove the placenta for at least 5 minutes, for bleeding seemed considerable. Only 4 were delivered in 2 minutes, 3 in 3 minutes; 6 were left longer than 5 minutes. The placenta was found in the vagina in 1, in the cervix in 17, lower uterine segment in 19, and in the fundus in 13. If early attempts had not been made to remove the placenta at the end of 2 minutes, fewer would have been found in the fundus. Total blood loss was very little more than in the other groups: 50 cc. or less in 35; 100–200 cc. in 6; and 500 cc. in one case where the placenta was adherent. Only 1 patient had a red cell count under $3\frac{1}{2}$ million, and only 4 a hemoglobin of less than 10 grams.

When oxytocics were given before delivery of the placenta, separation was more rapid and the placenta was usually delivered in 2–3 minutes; without oxytocics, 4–5 minutes. When ergotrate was given intravenously before delivery of the placenta, separation was more rapid than when pituitrin was given intramuscularly. When oxytocics were given early, blood loss was somewhat less. No patient was transfused during her hospital stay.

Manual removal of the placenta is not difficult, and there is much less danger in early removal, granted antiseptic conditions, than in allowing it to remain in the uterus for an hour or two. When done early, the patient is not in shock and has not lost an excessive amount of blood. Should placenta accreta occur, and bleeding be beyond control, hysterectomy can be performed without delay. If removal is delayed and done within the first 20–30 minutes, the routine vaginal antisepsis is still good protection. If routine antisepsis is not used, no amount of antiseptic can be effective once the vagina is filled with blood. In such cases penicillin and the sulfa drugs should be used; they are not necessary otherwise.

wherein these concealed hemorrhages have appeared before delivery, in spontaneous deliveries without episiotomy or laceration, and in operative deliveries. One more case is presented here.

The 31-year-old white housewife, gravida 2, para 0, was admitted February 7, 1946, for a study of hypertension of 14 years' duration, complicated by an intrauterine gestation of ten weeks. Although she was told of the dangers and advised that the pregnancy be interrupted, she strongly desired and was permitted to carry the fetus to term. Blood pressure ranged from 170/98 to 190/110 during the prenatal course. Moderate edema of the ankles, with a gain in weight, noted from time to time, responded to rest in bed, small doses of magnesium sulfate, sedation, restriction of fluid intake, and avoidance of salt. The urine was consistently negative for albumin; numerous white cells, microscopically seen, were attributed to a Trichomonas vaginalis infestation. Patient's subjective complaints were largely restricted to the effects of hypertension, i.e., headaches, dizziness, and "pounding" in the back of the head.

On September 4, 1946, patient went into labor. Blood pressure was 200/100. After an uneventful 6-hour first stage there followed a 40-minute second stage, completed by "outlet forceps" and a right mediolateral episiotomy with no extension. The third stage, 3 minutes, was normal. The infant was a well developed female weighing 8 pounds 13 ounces, who cried spontaneously. During the episiotomy repair, two large varicosities were noted deep to the levator ani muscles. These were not ligated but the sutures bringing the severed levators together were carefully placed superficial to the veins. No ooze was noted in the repaired perineum. One hour after delivery the fundus was firm and the lochia appeared normal. The patient was then fully awake and felt and looked well.

The following day, questioning disclosed perineal pain beyond so-called normal. Inspection disclosed a large hematoma involving the right side of the perineum, extending about 5 cm. lateral to the ischial tuberosity, and in the vaginal wall anteriorly to the urethra and posteriorly past the cervix to the broad ligament. The right side of the vagina was ballooned medially, reducing the lumen to a scant two fingerbreadths. Since it was believed that bleeding was continuing into the hematoma, immediate incision and drainage were decided upon.

Under cyclopropane anesthesia, the episiotomy was broken down and 500–600 cc. of clotted blood, mostly deep to the levator muscles, were removed. The multiple small bleeding points, evident only after the meticulous removal of all clotted blood, were ligated and the wound closed in layers using chromic # 1 catgut for the mucosa, fascia, and skin. Because of a moderate generalized ooze which could not be controlled by ligation, the vagina was tightly packed with plain gauze and external counterpressure created by a tight T-binder, with a Foley catheter into the bladder. During the procedure 1000 cc. of citrated blood were administered. Patient withstood the operation satisfactorily. Since a slight steady ooze of blood was seen on removal of packs the next day, the vagina was gently repacked with plain gauze which was in turn removed 6 hours later without mishap. Penicillin, 200,000 units, was given daily in divided doses for

PUERPERAL SEPSIS

THE INTERNATIONAL CONGRESS, ROTUNDA BICENTENARY

Rotunda Lying-in Hospital, Dublin

Lancet, 2: 102, 1947

At the time the Rotunda Lying-in Hospital was founded, Bigger said, in opening this discussion, puerperal sepsis was not very prevalent, because each midwife had a limited clientele.   Bringing patients to hospital exposed them to greater risks.   Today infection comes not from the doctor's hands but from some breach in the patient-to-patient barrier.   Group A hemolytic streptococcus, harbored in the throat and spread chiefly by droplets and dust, is considered chiefly responsible.   Use of penicillin for women carrying this organism at parturition, weekly throat checks and exclusion (until safely negative) of personnel in whom Strep. pyogenes are found, and, ideally, separate cubicles or rooms for each woman are among precautions suggested.   Puerperal sepsis is likely to become rarer, but the danger exists as long as Strep. pyogenes inhabits throats.   Even before the introduction of sulphonamides and penicillin, stated Gilliatt, the virulence of hemolytic streptococci was decreasing, and it may increase again.

Others pointed out that infection of the genital tract from the throat does not explain why many mishandled patients escape infection.   The resistance of the patient, and conditions such as prematurity and stillbirth, are important in development of sepsis.   A special unit in a separate ward, or preferably a separate fever hospital, is the most economical method of handling cases.

Also recommended are careful bacteriological investigation, use of sulphonamides if given at the first rise of temperature, and routine use of penicillin or sulfadiazine when instrumental delivery is undertaken after rupture of membranes or in presence of respiratory infection or skin sepsis.   Nixon believes a cesarean section less damaging in cases of prolonged labor than mutilating trauma in vaginal delivery; he prefers extra-peritoneal suprapubic lower-segment cesarean section, as done by Waters with 0.8 per cent fatality in 250 cases, in surgery for sepsis.   The absence of sepsis in China and Turkey leads him to wonder if we are losing our immunity.

POSTPARTUM PARAVAGINAL HEMATOMA

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Brooklyn Hosp. J., 5: 153–156, July, 1947

Although only 187 cases of paravaginal hematomas have been published since the first report in 1554, the condition is actually not so rare.   The physician's initial chagrin over such an occurrence may be dispelled by review of reports

vessels, tight closure with interrupted chromic catgut sutures, firm packing of the vagina and a T-binder. Therapeutic doses of penicillin were used prophylactically. The primary union obtained would warrant further trial of this method. The main contraindication for tight closure after evacuation of a hematoma, the "locking up" of a potentially infected area, may be altered by the efficacy of penicillin. Primary union is to be preferred to a closure by granulation tissue. The advantages of the method are twofold, the period of convalescence is greatly reduced, and the chances of ultimate relaxation of the pelvic floor are greatly lessened. ·

Early recognition of a paravaginal hematoma is essential, since subperitoneal extensions which may result in fatalities are apt to be discovered late and only after the patient lapses into a state of shock. A patient's complaint of pain in the perineum should not be ignored, especially during the first 24 hours when the analgesia of labor plus the anesthesia are still somewhat effective. Prevention is of course the keynote; the episiotomy wound should be regarded as a surgical wound to be treated with respect.

THERAPY IN PUERPERAL FEVER

Viktor Grünberger

The treatment in two cases of puerperal fever following manual removal of the placenta in the University Women's Clinic in Vienna are reported. The first ended in death of the patient, the other in recovery.

CASE 1

The patient, a 24-year-old primipara, gave birth to a 3,000 gm. daughter on April 23rd, 1938. After pituitrin and Credé's method had failed, the placenta was removed manually two hours later. The next day the patient suffered from chills and fever (39.7°C.). Treatment with cardiazol, chinin, salvochin and taurolin reduced the temperature to 38° in the next three days. Discolored, malodorous lochia persisted. The following day the chills and fever returned and despite administration of prontosil, pituitrin, gynergen, euthagen, caffeine and strychnin the temperature fluctuated between 37 and 39.5°C. until May 19th, when the patient was removed to the medical clinic because of edema of the lower extremities and a heart complaint, diagnosed as a sequel of sepsis. (The fever had been reduced temporarily on May 4th following the opening of a small abscess in the right gluteal region probably caused by the injections.) A transfusion of 500 cc. of blood was given on May 47th and two transfusions of fever blood on June 2nd and 10th, respectively. Treatment with drugs (pyramidon, cafféine, prontosil, and, for a cough, codeine) was continued but the edema of the lower extremities became worse, and the cough, pleural symptoms and fever persisted. Cultures of pleural fluid taken on June 22nd were aerobically and anaerobically

one week. The remaining postpartum course was satisfactory. Oral temperature rose to 101°F. for only one reading on the third postpartum day; since the breasts were soft, so-called "breast fever" could not be blamed, and the absorption of blood was believed responsible.

On the sixth postpartum day, there was temperature of 100.4°F. and pain and tenderness at the right costovertebral angle. A catheterized specimen of urine contained clumps of white blood cells suggesting a complicating pyelonephritis. Sulfathiazole, 1 gm. 3 times daily, was given. Temperature became normal two days later and remained so. Patient was discharged on the sixteenth day postpartum, with the perineal wound almost entirely healed, save for a small clean superficial separation at the mucocutaneous junction, and the uterus well involuted. During the puerperium, the blood pressure varied from 190/100 to 150/90. The consistently good output of urine had showed 1 and 2+ albumin and a tendency to fixation of specific gravity. The red blood-cell count was 3,000,000; the hemoglobin, 66 per cent; white count, 11,700, with polymorphonuclear leukocytes 83 per cent and lymphocytes 17 per cent.

Six weeks later, the perineum was well healed except for a small area of exuberant granulation tissue at the mucosal site of the perineotomy which responded to cauterization with silver nitrate. The blood pressure, however, remained elevated and was 200/100 2½ months postpartum.

The incidence of vaginal hematomas has been variously reported, from 1 in 1,600 labors, to this instance of 1 in 12,495. Fundamental principles have been covered by DeLee and Greenhill (Principles and Practice of Obstetrics, Saunders, 1947), Hamilton (Am. J. Obst. & Gynec., 39: 642, 1940), Lubin and Horowitz (Am. J. Surg., 63: 272, 1944), and others. These hematomas have occurred after operative as well as spontaneous deliveries, with or without episiotomies or lacerations; in the presence of toxemias and in nontoxic patients; and with or without varicosities and blood dyscrasias. Bleeding from the upper end of the episiotomy wound has been noted on the eighth day postpartum, with no blood dyscrasia. Mortality rate has been given from 8.3 per cent to 12 per cent.

Numerous etiologic factors probably operate. Regardless of cause and apparent rarity, if the physician were to exercise greater care in repair of episiotomies, ligating actively bleeding vessels and treating small hematomas as they begin to form, the incidence would further diminish. More attention should be directed toward the perineum in the first few hours of the puerperium. Frequently "stitches" have been blamed for pain actually caused by a thrombosed or protruding, edematous hemorrhoid or possibly an unrecognized hematoma. In some cases the obstetrician became suspicious only after opiates failed. It would be preferable to examine the perineum first, rather than to prescribe analgesics hastily.

Several methods of treatment have been used with varied results: (a) expectancy, (b) evacuating of the hematoma, (c) removal of clots and insertion of drains, (d) ligation of bleeding vessels, (e) removal of clots and packing, (f) leaving the wound open, (g) aspiration by a cannula, and (h) use of sulfanilamide by mouth. Here the wound was handled by removal of clots, ligation of bleeding

HORMONAL TREATMENT OF DEFICIENT LACTATION: RESULTS WITH CRUDE ANTERIOR PITUITARY EXTRACT

Margaret Robinson

In a previous study by the author no obvious reason was found for failure of lactation in 40 per cent of women (Robinson, M.: Lancet, 1: 66, 1943). Although no clinical signs of endocrine dysfunction were noted at this time, a study of results of treatment during the puerperium, with crude anterior pituitary extract, alone and with other substances, followed. Milk yield was assessed by test feeds on the fifth and tenth days of puerperium and when the infants were four weeks, six weeks, twelve weeks and six months old and recorded as the mean daily output for the groups. In previous study of 500 untreated lactations failure before the sixth month of lactation was rare where the milk output was at least 10 ounces on the fifth day of the puerperium and at least 16 ounces on the tenth day. These levels were therefore taken as the standard of establishment of lactation on the puerperium.

One hundred and twenty-six patients were studied in random distribution among four types of hormone treatment, three different types of non-hormonal treatment as controls and an untreated group as further control. If, after test feeding and according to the above criteria, there was failure to establish lactation on either the fifth or tenth day, experimental or control treatment was given daily until the thirteenth day, except for injections, which were given for five consecutive days only. On the average treatment began on the seventh day of the puerperium and ended on the thirteenth day.

Hormone preparations were given as follows:

(1) Injections of crude ox anterior pituitary extract,

(2) Injections of crude ox anterior pituitary extract plus 1 mg. hexoestral tablets four times daily by mouth,

(3) Injections of crude ox anterior pituitary plus dried thyroid gland B.P. 1932 gr. i four times daily by mouth, and

(4) Injections of crude ox anterior pituitary extract plus hexoestral by mouth plus dried thyroid gland by mouth.

The control treatments were as follows:

(1) Breast massage as advocated by Randall, M., *Training for Childbirth*, London, 1945, p. 87,

(2) Injections of physiological saline, and

(3) Administration by mouth of a proprietary galactagogue.

In 7 of the 21 cases treated with crude ox anterior pituitary plus dried thyroid gland, the dried thyroid gland alone was continued after leaving the hospital. The results were no better than among the patients whose pills had been discontinued on discharge from the hospital.

The mean daily milk output before treatment was practically the same in the treated cases and the controls. The increase was the same but the output began to fall in the controls by the 28th day of lactation, in the treated cases after 6

sterile.   The patient died July 18th.   Autopsy revealed that the local infection in the genital region had healed and that death was caused by sequelae such as metastasized abscesses in the lungs, thrombosis of the right ovarian vein, and other complications.

<div style="text-align:center">CASE 2</div>

This patient was 26 years old and had a history of an operation for perforated appendix with sepsis in 1930 and a normal confinement in 1936.   The placenta was removed manually one hour after the birth of a 3,930 gram boy, on June 1st, 1938.   The first four days following the confinement the patient complained of undefinable stomach pains.   Her temperature fluctuated around 37.5°C.   Treatment consisted of prontosil, cardiazol, Cebion, pituitrin and gynergen; wet, hot compresses; and 500 cc. Ringer solution daily (drop enema).   On June 14th and for ten days later she suffered from chills and temperature fluctuations from 39 to 40°C.   Treatment with drugs (argotropin, prontosil, dextrose, digipurat, caffeine and strychnin; as well as Progynon B oleosum, pituitrin and gynergen) was continued.   On June 23rd a blood transfusion of 140 cc. was given.   The chills and fever subsided, but the process began again on July 6th (three chills and temperatures to 40.2°C.).   The patient was dismissed on July 31st, with a somewhat resistant parametrium on the left side, but otherwise with normal gynecological findings.

Altogether, there were 7 deaths from puerperal fever in this clinic between 1937 and 1946.   The 6 deaths not reported here in detail, are commented upon briefly.   These cases were complicated with conditions such as endometritis, salpingo-oophoritis, uterine death of fetus, tuberculous pleuritis, metastasized lung abscesses, and thrombophlebitis of the uterine or ovarian veins.

The cases presented represent examples of the usual procedure in this clinic for treatment of puerperal fever.   At the present time penicillin and other drugs not available during the war are being tried.

(These two case reports bring to mind the high maternal mortality which followed manual removal of the placenta years ago.   It is now rather generally agreed that those high fatality rates were attributable to the employment of the procedure, almost exclusively, as a last resort operation on patients who were already exsanguinated and infected. The prognosis was probably aggravated, moreover, by repeated and brutal attempts with Credé expression,—a manoeuvre which might well be relegated to the limbo of obstetrical history.   In any event, such cases as the above are not to be construed as contradicting the opinions expressed by Dieckmann and by Mayes on pp. 44 and 46 of this issue, but they should nevertheless make us wary.—Ed.)

THE NEWBORN

FOETAL AND NEONATAL MORTALITY

Neonatal mortality, still 5 per cent in Dublin, as it had been 200 years ago, was regarded as perhaps the most important subject discussed at the conference.

Induction of labor, which can increase fetal mortality if misused, was originally introduced in the interest of the child and in selected cases lowers mortality. Branstrup of Copenhagen has used castor oil, oxytocin, and quinine sulphate effectively in 65 per cent of 407 cases, and when this failed, has employed rupture of membranes. For severely contracted pelvis cesarean section is preferable. Browne believes that induction has often been misused in England, and, furthermore, that cesarean section does not solve all difficulties: the child gains something by vaginal delivery, which causes a gradual increase in asphyxia—an excellent stimulus to respiration. Regarding toxemia, he protests inducing labor to save the mother from cardio-vascular injury, believing rest in bed best for bringing the pressure down. Greenhill likewise disapproves of early induction of labor for contraction.

In New York and Chicago hospitals, Greenhill reported, the main causes of neonatal deaths are anoxia, primary prematurity, congenital malformations, and birth trauma. For prematurity, the only preventable causes were those associated with toxemia; analgesics and anesthetics should be used as little as possible during delivery, and nursing is the main factor in survival. Birth injury is usually due to bad treatment or carelessness. Asphyxia in utero must be prevented; greater use of local infiltration instead of anesthesia, and oxygen to the mother, are suggested.

Corbett recommends keeping babies close to their mothers. Nurseries may lead to epidemics.

German measles convalescent serum to protect pregnant women exposed to German measles has been used by Ten Berge. He suggests prophylactic gamma-globulin in the first two months of pregnancy.

Baird's main contention was that infant mortality is an index of living and social conditions. The stillbirth-rate begins to rise at age 20 in the lowest social group, but not until 30 in the highest. The war brought a dramatic fall in the stillbirth-rate in all classes in every group. The importance of the mother's nutrition is especially emphasized, and early marriage, a reasonable number of children, and good care during pregnancy are mentioned as the ideal. 1 table.

weeks of lactation. The percentage of infants who were still being breastfed at six months was almost twice as high among the treated cases as it was among the controls. The best results were obtained with crude ox anterior pituitary plus dried thyroid gland, where 38 per cent of the infants were still being breastfed at 6 months as compared to the next best of 27 per cent breastfed at 6 months following massage.

In the untreated controls the breast milk had dried up by three months. Where hexoestral was given the results were no better than the controls, as was true with the crude ox anterior pituitary extract alone. Further investigation is suggested to determine whether the 100 per cent increase in output with the dried thyroid gland was due to the thyroid substance alone. 1 table.

RUBELLA AND PREGNANCY

ROBERT SANDERSON

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Brit. Med. J., **1**: 199, 1947

This letter tells a personal experience relating to an earlier article in the journal (Nov. 23, 1946, p. 778). The writer's grand-daughter is a deaf-mute. The child's mother had German measles in the third month of her pregnancy. An excellent little school was found in Cuckfield, Sussex, in which there are 15 deaf-mute children, all the same age and all apparently victims of a rubella epidemic of 1940. In 13 of the 15 there is definite history of the mother having had German measles in the early months of pregnancy. The author feels that this is strong evidence on etiology, and advocates inducing abortion, which he understands is being done in Australia.

STUDIES IN RH-ISOIMMUNIZATION IN PREGNANCY: OBSERVATION IN A SERIES OF NINETY-SIX SENSITIZED WOMEN

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Am. J. Obst. & Gynec., **54**: 400–414, September, 1947

During the first 13 months of operation of this laboratory, Rh typing was performed as a routine part of prenatal care on 12,410 women. One hundred and thirty-five additional known Rh-negative women were referred for detailed serum studies. The distribution of Rh types in the former group conformed closely to previously established ratios.

In a group of 1,635 Rh-negative women whose husbands were Rh positive, 86 instances of isoimmunization, or 5.26 per cent, were observed. Among 1,356 RH-negative women there were 727 primigravidas and 908 multigravidas. Nine instances of isoimmunization, or 1.24 per cent, were observed among the primigravidas. Seventy-seven sensitized multigravidas were observed, an incidence of 8.48 per cent.

Nine instances of isoimmunization were encountered in women belonging to types Rh' or Rh''. This constituted a theoretically calculated incidence of 5.7 per cent. It was noted that individuals of these blood types behaved, to all intents and purposes, as if they were pure Rh negative. One instance of Hr. isoimmunization was encountered in a group of 10,500 Rh-positive women.

FURTHER OBSERVATIONS ON DENTAL DEFECTS IN INFANTS SUBSEQUENT TO MATERNAL RUBELLA DURING PREGNANCY

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German measles occurring in mothers during the first 3 months of pregnancy is responsible for a number of congenital defects in the offspring, the most important being deaf-mutism, heart disease and cataract. In the present investigation dental abnormalities in a group of 45 children whose mothers had contracted rubella during the first trimester are given in detail. The main considerations in this analysis were time of eruption of teeth, degree of dental caries and degree of enamel hypoplasia.

The children were divided into 3 groups according to the period of pregnancy in which their mothers suffered from the infection. In Group A the period included up to 6 weeks. Infection occurred in this group before the teeth had commenced to form. In Group B (6th to 8th week) the infection took place as the dental papillae were being laid down. In Group C (8th to the 12th week) infection occurred at a slightly more advanced stage of tooth development. In 22 out of the 45, or 1 child in 2, there were varying degrees of retardation in tooth eruption. In 6 children the abnormalities were considered severe. The first tooth appeared sometime between the 12th and 24th month of age. Dentition was found to be incomplete in follow-up examinations at 2½ years to 4 years of age. In general this retardation of eruption was the most striking abnormality of the study and occurred with greater frequency in Group A children.

Three cases showed congenital absence of the incisor teeth (confirmed by x-ray). Four had eruption of permanent teeth before completion of deciduous dentition. This latter finding is considered quite unique in dental literature. Fourteen children had dental caries of varying degrees. This number is higher than one would expect in a similar age group selected at large in South Australia. The children in Group B had the highest incidence of dental caries. Since tooth formation is just beginning between the 6th and 8th week, rubella infection in the mother at this critical point would interfere with the formation of teeth. Thus the groundwork for dental caries is probably laid at this time.

Thirteen children exhibited enamel hypoplasia of different degrees. Teeth were usually affected in pairs and only 2 to 4 teeth were involved as a rule.

The sex of the child had no bearing on the incidence of abnormalities. The divergence from normal of tooth and arch formation was not pronounced.

KERNICTERUS: A FOLLOWUP STUDY OF THIRTY-FIVE ERYTHROBLASTOTIC INFANTS

RALPH STILLER

The author reviews the literature in which developed the concept of "kernicterus" or "nuclear jaundice" as a bile staining of ganglion cells damaged by ischemia or trauma and characterized clinically by the early appearance of jaundice with signs of involvement of the central nervous system. The infants that do not die then often show later mental retardation and symptoms associated with injuries to basal ganglia or extrapyramidal spasticity, athetoid and choreiform movements and emotional instability. Only a small percentage showed kernicterus post mortem. Later reports established the concept of "erythroblastosis fetalis" and then the etiological significance of Rh isoimmunization. Other reports have shown a high incidence of neurological sequelae running to 5 of 38 patients who showed erythroblastosis while, in this report, 6 of 7 that died showed this lesion at autopsy. (Docter, J. M.: J. Pediat., 27: 327, 1945.) Recently Wiener has explained the damage as due to anoxia following plugging of brain capillaries with agglutinated red cells. The ganglion cells then die and are stained by bile in circulation. (Wiener, A. S., and Brody, M.: Science, 103: 570, 1946.)

In this study were included 35 cases in which occurred the typical pattern of an Rh-positive child born of an Rh-negative mother, with the presenting complaint of either neonatal jaundice or anemia. Four were Negro, the rest white; six of the 35 have died. Of the 6 who died 2 showed cerebral involvement that might be construed as being related to kernicterus while one showed clinical involvement of the central nervous system but no characteristic pathologic changes. These confirm the discrepancy between clinical and pathologic changes as seen in the literature.

Twenty-nine of the 35 patients are living. Four have failed to develop normally and these case histories are presented in detail. There does not seem to be any correlation here with regard to degree of jaundice, intensity of anemia, number of transfusions given or physical findings. None of these children was first-born and the last case was the ninth child following eight normal deliveries. The last previous delivery had necessitated several transfusions for the mother and the blood had not been Rh typed. None of the 25 normal children showed any involvement of the central nervous system in the neonatal period; two of the four who failed to develop normally did show such involvement. The conclusion is drawn that the great majority of erythroblastotic children who survive will go on to develop normally.

The author warns that transfusion therapy can only be expected to aid in cases with anemia and is of no advantage in preventing brain damage specifically. 2 tables.

Erythroblastosis fetalis occurred in the offspring of 53, or 67.1 per cent of 79 isoimmunized women. Erythroblastosis fetalis was absent in the infants of 26, or 32.9 per cent, of this group. The fact is emphasized that the presence of Rh-isoimmunization is not necessarily synonymous with hemolytic disease in the offspring.

Erythroblastosis fetalis occurred once in 215 deliveries, an incidence of 0.46 per cent, in the total group of 12,275 women studied.

Antibody specificity was studied in 38 cases. Anti-Rh immune bodies were found in 32. Four patients had antibodies of Rh specificity; one, anti-Rh; and one, anti-Hr. In 65, or 67.7 per cent of 96 patients only univalent antibodies were found. Twenty-three, or 24.1 per cent developed only bivalent antibodies. Eight, or 8.3 per cent, showed a mixture of both varieties.

Fifty-five patients were studied in an effort to correlate prepartum antibody titers with outcome of pregnancy. When serum conglutination titers exceeded 10 units a significant infant mortality was noted. In 40 patients who were studied by the plasma conglutination technique, significant infant mortality occurred only when maternal titers were somewhat higher.

In a group of 49 patients in whom repeated prepartum serum studies were made several categories were observed: (a) 16 patients changed from a nonimmunized state to one of sensitization. In 11 this occurred in the last trimester; (b) 11 patients who were immunized when first studied showed a significant rise in titer during pregnancy; (c) 22 patients displayed no titer increase during the entire prenatal period. A distinct correlation between maternal serum titers and neonatal disease was demonstrated in most instances.

The influence of labor on antibody titer was studied in 19 patients. Eleven or 57.8 per cent, showed a significant rise in titer.

The duration of existence of the prepartum isoimmunized state, although of significance, was felt to be less important prognostically than the antibody titer.

Eighteen patients who were observed 1 to 60 months postpartum were demonstrated to still have antibodies in the circulating blood. The significance of this fact for transfusion therapy and subsequent pregnancies was noted.

Of 96 isoimmunized women, 10 were primigravidas and 86 multigravidas. Six of the 10 primigravidas had a definite history of previous transfusion. In 48.8 per cent of the multigravidas, the initial evidence of isoimmunization occurred with the second pregnancy. Initial isoimmunization in the remaining 51.2 per cent was scattered from the third to the eleventh pregnancy.

terribly sick and present complicated medical problems; 50 per cent of them die. Furthermore, the majority of infants with erythroblastosis seen here during the last two years have been born to mothers sensitized by blood transfusions. The few born to mothers sensitized by previous pregnancies have all been mild, presenting no serious problems.

STAPHYLOCOCCIC PEMPHIGOID DISEASES OF NEWBORN AND INFANTS

Sepp Tappeiner

Wien. klin. Wchnschr., 59: 372–376, June 1947

Data on cases of pemphigus treated at the University Clinic in Vienna from 1935 through 1945 are presented. In 1935 only one infant with pemphigoid disease was treated and in the following three years there were no cases. The 25 cases treated from 1939 through 1945 are listed by year, with pertinent data concerning sex of patient, site of first manifestation of infection, time of year, degree and duration of illness and type of disease. Twenty-three cases were of the bullous type and 2 were of the exfoliating type. Sixty-four per cent of the patients were girls. Only 10 cases occurred within the first 8 days of life; as a rule the bullous type is found most frequently in the newborn. A definite first site of infection could not be generalized for this group. Under favorable conditions the disease usually cleared up within 2 to 4 weeks. Cultures were taken in 8 cases; Staphylococcus pyogenes aureus was found in 7 and Staphylococcus pyogenes albus in the eighth. About 50 per cent of the cases occurred in summer; the other half during cold weather. There was a mortality of 8.3 per.cent. This figure includes one infant which was moribund when brought to the clinic and died two days later. The 2 infants with severe exfoliating pemphigus survived. None of the deaths occurred in summer. Sulfonamide powder or, preferably, salve, together with oral administration of sulfonamide tablets to the mother and sulfonamides dissolved in liquid to the infant, was found effective. Penicillin was not obtainable.

The author concludes that lowered standards in puerperal care and infant hygiene are responsible for the accumulation of 25 sporadic cases during the years of war and its aftermath. Oral confirmation of this was received from staff members of maternity homes in Vienna who reported not only a greater frequency of sporadic and endemic case of bullous and exfoliating pemphigus in infants, but also increased susceptibility of adults to pyogenes skin infections. Twelve cases of the disease in infants treated at one of the largest infant clinics in Vienna were traced to the same maternity home.

THE IMPLICATIONS OF RH INCOMPATIBILITY IN TRANSFUSION OF WOMEN

Louis M. Hellman

Department of Obstetrics, Johns Hopkins Hospital

Bull. Johns Hopkins Hosp., **81**: 73–74, July, 1947

The 9 Rh-negative women presented had received transfusions and subsequently delivered children with erythroblastosis or developed antibodies which endangered their further childbearing. Prior to transfusions, these women had 5 normal children; after, only two, both Rh-negative children of women with heterozygous husbands. Of the 8 children born to patients with homozygous mates, none was normal and only the expected 50 per cent survived. The future childbearing of all these women, especially of those with homozygous husbands, has been seriously jeopardized. At least one of the latter has consequently asked and received sterilization.

Although all but 3 of these patients had one or more pregnancies, which might have immunized them, prior to transfusions, it is worth noting that "a history of previous transfusion occurs in but 2 per cent of our patients, while in the 27 instances of erythroblastosis a history of transfusion was present in 7 women or 26 per cent." With the increased use of transfusion, the chances of unwittingly giving Rh-positive blood to Rh-negative females has definitely increased. It would appear highly negligent to transfuse a female child or woman in childbearing age without first determining the Rh-compatibility. In view of the apparent importance of transfusion in the production of erythroblastosis, this certainly seems the very minimum of care to be expected. For some time now no transfusion has been given in the Johns Hopkins Hospital to individuals of either sex without first determining Rh-compatibility, except in dire emergency, when Rh-negative blood is always used.

In discussion, Dr. Eastman pointed out the increasing importance of the role that transfusions rather than repeated childbirths play in causing stillbirths and neonatal deaths. An Rh-negative woman married to an Rh-positive man can have baby after baby sometimes without any dire results; because the Rh-positive cells do not find their way through the placenta, or for other reasons, she is not immunized. But in such a marriage, if the mother has a history of transfusion, the chances are nine out of ten that she will get into difficulty and will have been rendered unfit for childbirth. As statistics for Chicago in 1944 show, stillbirths and neonatal deaths due to erythroblastosis now exceed those due to syphilis. Anyone who has to do with the transfusing of females, whether they be a few hours old or 45 years old, should consider that the chances are one to seven or eight that the transfusion is Rh-incompatible. Accordingly Rh cross-matching should be done.

From the pediatrician's point of view, Dr. Janet Hardy emphasized that these erythroblastotic babies whose mothers were sensitized by transfusions tend to be

terribly sick and present complicated medical problems; 50 per cent of them die. Furthermore, the majority of infants with erythroblastosis seen here during the last two years have been born to mothers sensitized by blood transfusions. The few born to mothers sensitized by previous pregnancies have all been mild, presenting no serious problems.

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IMPETIGO NEONATORUM CONGENITA: FIVE CASES IN SIBLINGS

ABRAHAM GILNER AND IRVING NELSON

The authors review the literature on pemphigus neonatorum, or impetigo neonatorum congenita, and find it to be a rather rare condition. The first review in 1908 reported thirteen cases going as far back as 1794. Several reports have appeared since that time elsewhere and in the American literature bringing the known number of cases to thirty-eight with most of the later cases reported as neonatal deaths.

A case report is presented in which a 34-year-old colored patient delivered spontaneously a nine-pound girl on August 1, 1946. Immediately after delivery marked maceration of the infant's skin was noticed, with desquamation around the posterior portion of the neck extending to the angles of the jaw and also involving a small portion of the upper anterior chest, extensor surface of the right forearm and palms and soles. Several vesicles about $2\frac{1}{2}$ mm. in diameter were scattered on the left anterior chest and lower back. No lesions were present around the anus, mouth or eyes. General physical condition was excellent, laboratory findings normal, cord Wassermann and Kline negative. Staphylococcus aureus was grown from the vesicle fluid on 2 occasions. The baby's general health remained good. New crops of vesicles appeared at two- to four-day intervals, sparing only the lower chest and abdomen. These would rupture within the following 24–48 hours with localized desquamation subsequently occurring. Oozing and maceration of the skin were quite marked in the skin folds and crusting was marked on the scalp. X-rays of the long bones, wrists, and ankles were normal. At discharge, 5 weeks after admission, there was present, however, only a slight crusting of the scalp and a pigmentation of the upper and lower extremities.

History obtained from records revealed that the mother had given birth to normal babies in 1936, 1939, 1943, 1944. In 1937 and 1938 she had two spontaneous abortions. In October 1936 she was found to have a slightly or questionably positive serological test for syphilis. She was given treatment for one year, then discharged as cured. Since 1938 the mother had been subject to outcroppings of small blisters around her neck and, regardless of treatment, these would heal and then reappear, becoming worse with each succeeding pregnancy and for four to five weeks following time of parturition. All of the normal babies delivered had vesicles, skin maceration of small bullae on the skin and in all the cord Wassermann and repeated Wassermanns were normal.

The congenital form of pemphigus neonatorum is, as a rule, benign, does not affect the general condition and heals within a few weeks with no scarring, no recurrences. The problem of etiology is obscure. Congenital syphilis seems to be ruled out. Two of the cases reported here showed staphylococci, one showed gram positive diplococci. The mothers in the cases reported in the literature

were normal, without lesions, whereas the authors feel that in these cases there must have been a close relation between the mother's lesions and those of the siblings.

A COMPARISON OF VITAMIN C IN MOTHERS AND THEIR PREMATURE NEWBORN INFANTS

LAWRENCE B. SLOBODY, REUEL A. BENSON, AND JOAN MESTERN

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Reports in the literature indicate that newborn infants have a higher vitamin C concentration in both tissues, as shown by intradermal tests, and plasma, than their mothers have. The similar results in both tests suggest that the fetus takes its supply of vitamin C and tends toward saturation, whether or not the mother has a sufficient amount.

Few tests have been done on premature newborns. Urine tests in one study indicated at 10–15 days of age less saturation than in normal newborns, but no connection between degree of saturation and body weight, and no influence of increased vitamin C intake on the development. Levine and co-workers (J. Clin. Inves., 20: 209, 1941) demonstrated that premature infants on vitamin C free cow's milk containing 5 gm. or more of protein per kgm. exhibited a spontaneous defect in the intermediary metabolism of aromatic amino acids, which could be eradicated by l-ascorbic acid without necessarily raising the plasma ascorbic acid levels. Prematures receiving human milk have been shown to retain a larger part of a saturation dose than those on cow's milk. It is suggested that an increased daily requirement for vitamin C is related to a high level of protein intake.

In the present study, mothers and their premature infants are compared for vitamin C by the intradermal test, a qualitative test based on the intradermal injection of a dye, which will be decolorized by vitamin C. A skin test time (time for disappearance of the dye) of 14 minutes or more indicates a definite degree of tissue unsaturation; 10–13 minutes is borderline, and less than 9 minutes indicates a normal amount of vitamin C in the body tissues.

The test was done in duplicate on 30 mothers and their premature infants as early as possible, within a few hours to one week after birth. The intradermal test times for the disappearance of the dye were shorter in the premature than in the mother except in one instance. Average times were 4.9 minutes for the infants, 9.1 minutes for the mothers. All the infants were receiving evaporated

milk formulas, concentrated cod-liver oil, and vitamin B complex. The baby's weight had no relation to the test time.

Ten of the prematures were followed for about 8 weeks, on 25–100 mgm. of ascorbic acid daily, with weekly intradermal tests. Weights were taken every other day. Vitamin C concentration remained good in all the prematures, those receiving 25 mgm. of ascorbic acid daily comparing favorably with those taking large doses. All gained weight. The clinical impression that those receiving 50 mgm. or more daily gained better than those receiving 25 mgm. could not be statistically confirmed in such a small series.

The 9.4 average time for 77 mothers in a previous study of normal newborns is very similar to the 9.1 minutes in the mothers of prematures. This contradicts the suggestion that vitamin C deficiency of the mother has a role in the occurrence of premature births. Test times for the infants—average 5.0 for the full-term and 4.9 for the premature infants—also indicate that the mother-infant relationships are very similar. In the prematures as in the others, the infants had a good tissue concentration even when the mothers were depleted.

Evidence has been presented that the placenta selectively retains vitamin C in the fetus. (Lund and Kimble: Am. J. Obst. & Gynec., **46**: 635, 1943.) It is further suggested here that the fetus nervous-humoral control for vitamin C is set at a higher level than that of the mother.

The intradermal test is of course qualitative rather than quantitative. However, in preliminary blood studies of thiamine, also a water-soluble vitamin, the premature seems to have as good a concentration as the normal newborn.

In view of the work reviewed, and since the premature does have a more rapid metabolism than the full-term newborn, it appears wise to start ascorbic acid probably in the first week of life. 50 mgm. daily gives good tissue concentrations. 2 tables.

DIET OF MOTHER AND BRAIN HEMORRHAGES IN INFANT RATS

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Female rats were reared to maturity on a synthetic diet that was deficient in vitamin K. If lard was removed from their diet and the females allowed to bear litters, a high incidence of brain hemorrhages occurred in the offspring. The hemorrhages did not occur when the diet contained either lard or vitamin K.

The incidence of hemorrhage in first litters was 34.5 to 44.17 per cent and in subsequent litters, 73.7 per cent.

Most of the young that died with brain hemorrhages were either born dead or

died within 24 hours after birth. A few young in the first litters developed hemorrhages between the eleventh and twenty-first days.

The whole blood coagulation time of females which produced hemorrhagic young and of young with visible hemorrhages was normal. This shows that the prothrombin level was not abnormally low and it is suggested that some substance which acts normally to maintain capillary strength is not synthesized by the body when the diet is low in fat and deficient in vitamin K. An assay with chicks shows that lard may contain a small but insignificant amount of vitamin K.

OPERATIVE OBSTETRICS

INDUCTION OF LABOR AT THE CHICAGO LYING-IN HOSPITAL

WM. J. DIECKMANN AND ROBERT B. McCREADY

The Department of Obstetrics and Gynecology, The University of Chicago, and The Chicago Lying-In Hospital, Chicago, Illinois

During the thirty months ending June 30, 1943, there were 8,503 deliveries at The Chicago Lying-in Hospital and 618 attempted inductions of labor, an incidence of 7.3 per cent. There were 136 failures with castor oil and quinine which are not included; 20 with S.O.P.P. (Solution of Posterior Pituitary); four after rupture of membranes; and one after rupture of membranes, traction on bag and S.O.P.P. One hundred eighty-three histories were deleted because, although delivery occurred, the latent period after rupture of the membranes was less than one hour or longer than 12 hours after injection of S.O.P.P. Thus, 267 patients (3.2 per cent) had an induction of labor and 342 patients (4 per cent) had the pregnancy artificially terminated. The incidence of failure was 9 per cent.

The reports published since 1930 demonstrate that although there has been a decrease in the fetal and maternal mortality due to induction of labor, it is still a significant figure. The uncorrected fetal mortality ranges from 0 to 37 per cent, and the maternal from 0 to 2.8 per cent. The corrected mortality figures are much less, but still as a rule higher than the normal percentages. Browne reported that 5 per cent of 173 maternal deaths in nine British maternity hospitals staffed by experts, followed directly on induction. The figures for maternal morbidity are 3 to 25 per cent. Since the average morbidity in most maternity hospitals is 7 to 10 per cent, it is obvious that the morbidity is increased with its inevitable residual damage from puerperal infection. The number of failures to initiate labor ranged from 0 to 30 per cent.

Gillet, in 1944, reported a thousand consecutive inductions of labor without any failures. Labor began in all cases within twelve hours. There were no maternal deaths and no stillbirths. There were eight neonatal deaths none of which were attributable to the induction. Even though all the cases were very carefully selected, this is an unusual record.

Induction of labor is indicated in comparatively few cases as compared to twenty-five or more years ago when the cesarean section mortality was 10 per cent or more. The primary indication must always be: is the patient better off with the uterus empty; or if the infant is alive and in good condition, is its chances of survival increased by early delivery?

The authors review their indications for induction of labor as follows:

Placenta Previa. If there is some cervical dilatation and if the previa is not a total one the authors rupture the membranes. If the bleeding cannot be controlled by rupture of the membranes with traction on the head or on the foot, they perform a cesarean section. They rarely use the bag or pack.

Abruptio Placentae. The authors rupture the membranes and usually these patients deliver very rapidly. During this period the patient is given adequate amounts of blood, and parenteral glucose and saline solutions. If the patient shows clinical improvement, nothing else is done. If, at the end of four to eight hours, there has been no change in the cervix and the patient on admission has presented evidence of great blood loss (indicative of complete separation and/or a Couvelaire type uterus), the case is again evaluated and a cesarean section may be performed.

Eclampsia. After the patient has been treated medicinally, which requires four to six hours, a vaginal examination is made and if there is any dilatation, the membranes are ruptured. Occasionally, a bag may be introduced to hasten delivery.

Nonconvulsive Toxemia. No one will debate but what the best treatment for toxemia is termination of pregnancy. However, in many of the patients, the toxemia is of such a degree that the pregnancy can be permitted to continue until the baby is near term or until the cervix is ripe. Certainly, severe toxemia at any time and especially after thirty-two weeks warrants termination of the pregnancy. The authors' practice for many years has been to evaluate the seriousness of the toxemia and its effects on both maternal and fetal life. When the toxemia patient is two to four weeks before delivery it is amazing how much change can occur in the cervix in seven to ten days' time.

From 1931 to 1936, 21 per cent of their toxemic patients were induced and 21 per cent had an abdominal delivery, a total of 42 per cent. By 1936, these figures were 14 and 9 per cent, respectively. Their fetal and maternal mortality in some 300 toxemic patients per year has been steadily decreasing primarily because of earlier recognition and treatment of the toxemia while it is still mild.

Systemic Disease. Certain cardiac patients who have been hospitalized and are compensated and in whom the cervix is ripe, usually have labor induced by rupture of the membranes. These patients should not be permitted to carry the baby any longer than is necessary. Furthermore, induction of labor permits the optimum time to be selected. Patients with pulmonary tuberculosis, severe anemia, or diabetes mellitus, should be induced, in general, when the cervix is ripe.

Habitual Intrauterine Fetal Death. The pregnancy is terminated at thirty-five to thirty-seven weeks by cesarean section or by induction, if the cervix is ripe.

Polyhydramnios. When the distention of the uterus causes cardiac and/or respiratory embarrassment, the membranes are ruptured. We have aspirated amniotic fluid through the abdominal wall, but many of these babies are abnormal and nothing is gained by continuing the pregnancy. An X-ray should

be obtained as soon as the fluid has been drained off and frequently an abnormal fetus can be detected.

Twin Pregnancy. Because of the overdistention, even though there may be 3 or more centimeters of cervical dilatation, the uterus may not contract. Rupture of the membranes, permitting as much fluid as possible to escape, will usually precipitate labor.

Convenience. In general, induction of labor should not be carried out for the convenience of either doctor or patient. Three patients were induced for the doctor's convenience. Twelve multiparous patients who lived a considerable distance from the hospital were sent in for rupture of the membranes when the cervix was ripe. This is proper obstetrics.

Ruptured Membranes. Patients with ruptured membranes are examined vaginally. If the cervix is ripe, they are given fractional doses of S.O.P.P. according to their routine. S.O.P.P. is not given after the membranes have ruptured for twenty-four or more hours because of the increased likelihood of uterine rupture. If the cervix is closed, or if there is a long canal, no further measures are carried out. The patient is sent to her room, permitted to be up and about, vaginal instillations of 1 per cent merthiolate in glycerin are made every twelve hours and in from one to fourteen days most of these patients will go into labor and usually have an uneventful delivery. There is some increased risk of infection for both fetus and mother, but their results for both are immeasurably better since they have discontinued the routine induction on all patients who had a spontaneous rupture of the membranes. They do not give sulfonamides and/or penicillin to these patients as a prophylaxis.

Cephalopelvic Disproportion. The authors have not induced labor for many years where there was any evidence of disproportion either from a contracted pelvis or from an abnormally large baby. With cesarean section as safe as it is today the fetus should not have its life jeopardized or suffer permanent injury by induction of labor. They prefer that these patients go into labor and, if at the onset of labor there is marked disproportion, the patient must have a cesarean section. If, after a careful test of labor according to their criteria, there has been no increase in dilatation or descent of the presenting part, they perform a laparotrachelotomy.

Postmaturity. There are no criteria by which postmaturity can be determined either before or after delivery. The authors believe that the cervix is the best index. They do not induce labor because patients are at term or because they are overdue. Those patients in whom there is evidence of disproportion because of the size of the baby are permitted to go into labor, kept "clean" and, if necessary, a cesarean section is performed after their test of labor.

Cesarean section was performed in five patients who did not go into labor as a result of either S.O.P.P. and rupture of the membrane or the additional use of volsellum in two cases (cesarean-hysterectomy). There were definite indications for the operations in all cases; placenta previa in two cases and disproportion in three cases.

There were two maternal deaths, one patient had an abruptio placentae and at

autopsy also had a cortical necrosis of the kidney, necrosis of the anterior lobe of the pituitary, and an eclamptic liver. Obviously the rupture of the membranes was not a factor. The other patient had been observed for some weeks and in view of the increasing severity of the toxemia it was deemed advisable to induce labor. The baby died in utero, the bag was expelled, and the uterus was ruptured by an inexperienced resident attempting to deliver an impacted shoulder in a baby weighing 1,600 grams. The death in this case was related in part to the induction.

There were 17 fetal deaths, but 4 of these weighed less than 1,500 grams. Three of the deaths were antepartum, two intrapartum (one from prolapse of the cord), two from major anomalies, one from toxemia, three from previa, and two from abruptio. The corrected fetal mortality was 0.7 per cent.

The authors' average hospital morbidity is 9 per cent. The morbidity in patients who were induced was 14.7 per cent (38 to 38.9°C.); 4.7 per cent (39°C.) a total of 19.4 per cent. There was only one serious case of pelvic thrombophlebitis (placenta previa). Eight patients had pyelitis, three mastitis, three respiratory infections, and one an infected episiotomy.

The senior author, during his training, had the opportunity of making frequent vaginal examinations and urges that this method of teaching be used more extensively. Certainly it is the only method which enables one to appreciate the importance of a "ripe" cervix for the successful induction of labor. The "ripe" cervix in the primipara is one in which there is complete effacement and the cervical margins are 0.5 to 1.0 cm. thick and soft. The dilatation varies from none to 3 cm. In the multipara the canal may or may not be effaced but in either case there is 2 or more cm. dilatation and cervix is soft.

If labor is to be induced with the most favorable outcome, a sterile vaginal examination must be made and the condition of the cervix determined. If it is ripe, one can be almost positive that the induction will be successful. At the time of the initial vaginal examination one must determine that there is not a forelying loop of cord or abnormal presenting part. If one contemplates a medicinal induction, the membranes should be stripped as high in the uterus as possible. The next morning the lower bowel is emptied by either a suppository or an enema and then either a medicinal induction with S.O.P.P. or rupture of the membranes is carried out. The authors' experience has been that the induction with S.O.P.P. will fail if the cervix is not ripe and dilated 1 or more cm. As a rule S.O.P.P. will not produce uterine contractions at any period of pregnancy unless there is some dilatation of the cervix.

In those cases where a bag is indicated, it is used. It may be a rectal, vaginal, extra- or intraovular bag. In general, the authors prefer to insert a bag large enough so that when it is expelled, the baby's head can follow. They attach no traction to the bag until eight to twelve hours after its insertion. They also do not use S.O.P.P. until the bag has been in place for eight to twelve hours.

(This article has been abstracted *in extenso* because it covers the management of so many conditions and sets forth succinctly the policies followed in one of our great obstetrical clinics.—Ed.)

ELECTIVE INDUCTION OF LABOR

R. M. Grier

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From November 1, 1935, through October 31, 1945, 10,439 women were delivered at the Evanston Hospital. Excluding bag inductions, 1,353, or 12.9 per cent, had their labors induced. In the first five of these years the incidence of induction was 10.9 per cent, and in the latter five years, 14.4 per cent. Because of this trend in their hospital, and because this procedure has been considered by some to be meddlesome obstetrics, it was believed that a study of the results should be made.

The author believes certain conditions should be present before the induction of labor is attempted especially when there is no therapeutic indication. He would like to re-emphasize these important conditions:

1. There should be no cephalopelvic disproportion.
2. The baby should be mature and should preferably present by the vertex.
3. The fetal head should be engaged or dipping well into the pelvis. It must not be floating or ballottable.
4. The cervix should be soft, partially effaced, and dilated to at least one centimeter. These are the signs which usually precede the onset of normal labor.

In short, the onset of labor should be imminent, and obstetric prognosis good, for the elective induction of labor.

Method of Induction

When the above conditions are found upon rectal examination, the patient is informed that she may go into labor at any time. She is told that if she so desires she may select a time in the near future for her delivery. This can be made at a time most convenient for herself, her family, and her husband, to say nothing of the physician. She can make arrangements for the care of her household. In these days this is an important consideration. If she has had precipitate labors in the past, a repetition of this experience can usually be avoided by inducing labor. The patient usually enters the hospital in the morning after a night's sleep at home in her own bed. She had been instructed to have no breakfast, as anesthesia is far safer when the stomach is empty. She is admitted in a happy frame of mind without confusion. The nurse, anticipating her arrival, takes her in charge without hurry, then gives her a careful perineal preparation and a hot soapsuds enema. Soon after this the intern gives her intravenously, 10 cc. of 10 per cent calcium gluconate solution. Usually within two hours the physician ruptures the members artifically. In some instances this is not necessary, as labor is so near that spontaneous rupture will follow the enema. Before the bag of waters is ruptured the perineum and vulva are cleansed with soap

and water and an aqueous solution 1:2,000 zephiran chloride is poured freely over the introitus. The rupture may be done with a sterile gloved finger in the vagina to guide a perforator through the cervical opening to the membrane. He often prefers to use a dressing forceps guided rectally. He believes this does not cause as much trauma and introduces fewer bacteria than rupture done vaginally. The use of a sharp pointed perforator is more likely to leave scratches on the infant's scalp, and possibly laceration in the vagina or cervix. Before rupture is attempted the obstetrician should be certain that a forelying cord is not present. If the presenting part is fitting well into the lower uterine segment, prolapse of the cord is almost impossible. The fetal heart tones should be observed before and frequently after artificial rupture.

If labor ensues within two hours, it is allowed to progress without further stimulation. If it does not, one minim doses of pitocin are given intramuscularly, being repeated at thirty- to sixty-minute intervals. Usually no more than two doses are required. In this series, 36 women went into labor without any need for pitocin. In none was any evidence of tetanic contractions observed.

Results

In the year August 1, 1945 through July 31, 1946, 1,284 women were delivered. There were 129 inductions, an incidence of 10 per cent. Only six of these were induced for therapeutic reasons. Four were because of severe toxemia, and two for marginal placenta previa. All the rest were considered elective inductions. There was only one which could be considered a failure. This patient was a multipara. It was thought by the physician that her membranes were ruptured artificially but they were not. This case was improperly chosen in that the head was entirely too high. She did go into labor and dilated to 7 centimeters. An x-ray revealed the infant was presenting by the face with the chin posterior. After eight and one-half hours of labor she was delivered by low cervical section.

Only five women in this series became morbid as measured by a temperature rise as high as 100.4°F. This is less than the author's incidence for all deliveries which is usually between 5 per cent and 6 per cent. Only one of these was febrile for four days.

There was one stillborn macerated fetus and one neonatal death. The latter was a baby two days overdue, weighing 2,620 gm., delivered spontaneously after a labor of two hours and eighteen minutes. Autopsy disclosed only fetal atelectasis. There were two breech deliveries, several manual rotations of the head when the occiput was posterior, and our usual incidence of low forceps and spontaneous deliveries.

Thirteen women were induced eight or more days before the estimated date of term. All of these were multiparas, and all the infants survived. Thirty-five were delivered within less than a week before term. The remainder were at term or beyond.

As a rule the labors were considerably shorter than has been the rule in his service. The average latent period for primiparas was 4 hours ±29 minutes, and for multiparas 55 minutes ±5 minutes. The longest latent periods for

primiparas were 22 hours and 15 minutes in one, and 8 hours in another. The longest latent period for a multipara was 6 hours and 30 minutes.

It is the author's contention that the more completely the conditions described above are fulfilled the more smoothly will induction and labor proceed. He compared the latent time and duration of labor in those women who have findings adequate for the induction of labor, such as slight effacement and only one centimeter dilatation of the cervix with those in whom these conditions were more advanced, namely moderate effacement to complete effacement and more than one centimeter dilatation of the cervix. There were 67 women in the former group. The time from the rupture of the membranes to the onset of labor was 1 hour 18 minutes ±11 minutes. However, in the latter group, there were 62 in whom the latent time was only 44 minutes ±6 minutes. The duration of labor in the former group was 6 hours 18 minutes ±39 minutes. In the latter it was 3 hours 33 minutes ±14 minutes.

The same statement as made in the above paragraph is true for another important condition, the station of the fetal head. In the first group are placed those in whom the station was from 1 centimeter above the ischial spines to 3 centimeters above the spines; while the second included those in whom the station was lower than 1 centimeter above the spines. In the former group there were 78 women in whom the latent period was 1 hour 36 minutes ±14 minutes. In the 51 in the second group, the latent time was only 29 minutes. The duration of labor was also definitely shorter. In the first group it was 5 hours 30 minutes ±4 minutes and in the second, 3 hours 34 minutes ±14 minutes.

EXPERIENCE WITH THE POMEROY METHOD OF STERILIZATION

WILLIAM F. NELMS AND MARGARET H. DOYLE

Department of Gynecology and Obstetrics, Brooklyn Hospital and Long Island College of Medicine, Brooklyn, New York

This paper is a report and study of all sterilization cases at the Brooklyn Hospital from January 1, 1929 to January 1, 1945. The Pomeroy method of sterilization was used exclusively during this 16 year period on a total of 404 patients.

The proper Pomeroy operative technique is very important. It consists of picking up the loose middle portion of the fallopian tube with a clamp, ligating a one to one and one-half inch segment of the loop with plain absorbable catgut, and resecting the portion of the loop distal to the ligature. The tube is not traumatized or crushed and the ligature is tied tight enough to prevent bleeding but not tight enough to cut into the tube. The tubal stumps are not cauterized.

One hundred and thirty-two cases in this series (32.6 per cent) were done at cesarean section; 108 (26.7 per cent) were sterilized at hysterotomy; and 164 (40.5 per cent) were done at gynecological operations. Only 7.9 per cent of the

patients were near the menopause at the time of sterilization (39 years of age or over).

The indications for sterilization were conservative. No patients had tubal ligation for social reasons, multiparity or on their request. The main reasons for sterilization were operations for prolapse or cystocele (136) and organic heart disease (130). The patients who had their second or third cesarean section (68) were next most common, followed by toxemia, eclampsia or kidney disease (26) and pulmonary tuberculosis (20). Mental or organic brain disease was an indication in 16, while 4 were sterilized for Raynaud's disease, 2 for chronic thrombophlebitis and 2 following repair of third degree perineal lacerations.

One failure occurred; an incidence of 0.24 per cent or 1 in 400. The followup in this series varied between 2 and 16 years and included 86.1 per cent of the cases. The failure case was of interest in that 13 years elapsed between sterilization and the pregnancy which terminated in a ruptured ectopic.

There were 2 serious complications; one of intestinal obstruction and one of hemorrhage from slipping and cutting of the ligature.

There were 3 postoperative deaths, 1 of eclampsia, 1 of heart disease and 1 of sepsis and hemorrhage. The last was the only death in which the operation was a contributory factor. It was considered preventable because the proper technique was not used.

POSTPARTUM HEADACHE AFTER LOW SPINAL ANESTHESIA IN VAGINAL DELIVERY AND ITS TREATMENT

Frederick Weintraub, William Antine, and Albert J. Raphael

Israel Zion Hospital, Brooklyn, N. Y.

Headache following the use of low spinal or saddle block anesthesia for vaginal delivery is an annoying though transitory complication in some cases. The incidence of postlaparotomy spinal headache in cesarean section and various gynecologic operations was found by us to be much lower than in vaginal delivery. In the latter, a headache incidence of 15 per cent was noted in a series of 300 cases. As the authors were unwilling to forego the many advantages of spinal anesthesia in obstetrics, as set forth in an earlier publication, the mechanism and treatment of the postpartum spinal headache became a practical problem, particularly since it was the only postpartum complaint attributable to the anesthetic. The higher headache incidence in vaginal, as compared with abdominal deliveries, indicated that there were certain factors concerned in its production which do not usually operate in cases subjected to cesarean section or other abdominal operations under spinal anesthesia.

In a very severe case of post lumbar-puncture headache, the patient, on stand-

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The more important factor in the initiation of the headache after spinal anesthesia the authors believe to be the pooling of blood in the splanchnic vessels induced by the sudden release of intra-abdominal pressure occurring postpartum, which is further augmented by the vasomotor paralysis due to the action of the spinal anesthetic on the sympathetic nerves. Though this was not evidenced clinically in all cases by the presence of orthostatic hypotension and/or tachycardia, the relief afforded by abdominal compression in both groups indicated that their ability to make the necessary compensatory vascular adjustments was faulty. The majority of patients (85 per cent) do not develop postspinal anesthesia headache because of a compensatory vascular competence, or minimum spinal fluid leakage, or both.

The authors' prophylactic orders for headache postpartum consist of (1) immediate postpartum application of a medium sized sandbag to the abdomen, (2) firm abdominal binder twenty-four hours postpartum to be reinforced by folded towels, particularly in the scaphoid abdomen. Frequent resetting of the binder to maintain firm pressure as the abdomen involutes or the patient shifts position, is essential for effective results. It is advisable to continue the use of the binder until the patient is discharged from the hospital on the seventh to the tenth day.

ing upright out of bed, experienced an accession of headache and throbbing in the ears, the pulse rate rose to 130 per minute, and the blood pressure fell to 60/0. This evidence of orthostatic hypotension and tachycardia suggested the application of firm, manual, abdominal compression. Amazing and instantaneous relief of symptoms followed. Release of abdominal compression was succeeded by prompt recurrence of headache and throbbing. A very tight abdominal binder was forthwith applied to maintain constant compression, and the patient was enabled at once to resume her usual duties unhampered by return of symptoms. This dramatic therapeutic result encouraged further investigation of its modus operandi, and the following routine was instituted.

Three hundred patients delivered vaginally under spinal anesthesia were questioned daily during the postpartum period for the occurrence of headache. As soon as any complaint was registered, the following observations were made:

1. Blood pressure reading and pulse rate lying in bed.

2. Blood pressure readings and pulse rates, one minute and three minutes respectively, after standing out of bed.

3. Effect of firm, abdominal compression on headache, blood pressure, and pulse rate in and out of bed.

As a control, similar observations were made on a group of puerperae in whom no headache had developed by the fifth postpartum day.

Of the 300 patients examined, headache occured in 45. It was noted that postpartum anesthetic headache in this group most often appeared on the third or fourth postpartum day. Twenty-three of the patients developing headache after spinal anesthesia (slightly over 50 per cent) exhibited orthostatic hypotension of varying degree which was in almost every instance associated with orthostatic tachycardia. No direct relationship was demonstrable between the degree of orthostatic hypotension and/or tachycardia and the intensity of headache. Individual emotion reaction and varying threshold for pain, in addition to certain unknown factors, are probably accountable for this finding. Abdominal compression, at first tentatively by hand to test immediate response, and then, by means of a tight binder, resulted in a complete, or almost complete, relief of postpartum puncture headache in most cases (90 per cent). A many-tailed, abdominal binder, extending from the symphysis pubis to the xiphoid process, reinforced by folded towels inserted between binder and abdominal wall, as required to maintain maximum continous compression, proved satisfactory. Frequently the patient's own laced, abdominal support, firmly applied, proved equally efficacious.

Determinations of blood pressure and pulse rates did not bear out the authors' early expectation that the headache was invariably associated with orthostatic hypotension and/or tachycardia. While all patients who exhibited orthostatic hypotension and/or tachycardia did develop headache, a considerable number (almost 50 per cent) complained of headache on the third or fourth postpartum day without evidence of a definite fall in blood pressure or marked rise in pulse rate. The essential point of practical application is that firm abdominal compression was efficacious in relieving the headache in either category.

It should be mentioned that a small incidence of postpartum headache and orthostatic hypotension and tachycardia are found irrespective of the use of spinal anesthesia. Chronic sinusitis, dental disorders, constipation, neuralgia, migraine, breast disorders, psychic, and other factors require differentiation in our experience. If spinal anesthesia be administered to patients in this group, the headache may be erroneously attributed to the anesthetic. If headache develops, firm abdominal compression should be applied in any case; and the headache, if it be of spinal anesthesia origin, will almost always be effectively relieved, while if it be of other origin, it will remain unaffected. If orthostatic hypotension and/or tachycardia is found, the headache is most likely of spinal anesthesia origin. Headaches of other origin were excluded from this study. There is a strong element of suggestion in the development of any postpartum headache, and the authors have learned from experience that it is wiser not to question for its onset too overtly, but rather by indirection, or to wait until the patient volunteers the complaint. A discreet nurse helps considerably, while injudicious questioning by attendants causes a higher incidence of this complaint.

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SOCIAL AND LEGAL ASPECTS

HUMAN FERTILITY IN PUERTO RICO

CHRISTOPHER TIETZE

Baltimore, Maryland

This article discusses the factors in the growth of the population in Puerto Rico since 1899 and the meaning of this relation to overcrowding and measures of fertility control. The population of Puerto Rico almost doubled, from 953,000 in 1899, to 1,869,000 in 1940. During this period the birth rate has remained virtually unchanged at about 40 per 1000 but the net reproduction ratio has steadily increased, supposedly due to decline of mortality and a vigorous public health program. The differential reproduction by residence and color is studied in terms of the "fertility ratio" or number of children under 5 years of age per 1000 women aged 15–49, with estimates of some figures unknown due to lack of census figures for 1899. Estimating a fertility ratio of 378 necessary for replacement gives a net reproduction ratio from 1935 to 1940 of 1.0 in San Juan, ranging to 2.0 in the rural territory. Study of the figures for 1899 gives approximately the same fertility ratio with the same distribution between urban and rural populations as in 1940 but with fertility ratios higher for whites than negroes in the urban areas in 1899. The author explains this unchanging reproduction ratio through the increase in the percentage of married women in the population counteracted by decrease in marital fertility of about 25 per cent from 1899 to 1940. The proportion married in urban areas in 1899 was much higher among whites than colored; about two-fifths of the urban colored women in 1899 were employed in domestic science and unmarried.

The author feels that a trend toward lower reproduction ratios is now being masked by war babies and the recent prosperous years for the islands. With the birth rate at a high level, however, and the death rate dropping from 18.4 to 14.0 per 1000 during the past five years, the population is increasing at an annual rate of 2.2 per cent. With over 600 inhabitants per square mile and 2 inhabitants per acre of arable land, Puerto Rico is one of the most densely populated areas in the world and is about half as wealthy as our poorest state, Mississippi, in terms of per capita income.

Many attempts have been made to control population as well as to increase industrialization and use of resources. Contraceptive materials have been sold for a long time, but the first organized efforts to disseminate birth control information began in 1925. Seven years later two clinics were opened for a short time. In 1935 Gladys Gaylord of the Cleveland Maternal Health Association introduced a contraceptive program into the activities of the Puerto Rico Emer-

gency Relief Association. Though the results obtained were very encouraging, the federal agencies again left birth control work in private hands. The Asociación Pro Salud Maternal e Infantil de Puerto Rico opened clinics and carried on research work, curtailing its activities only after the Insular Health Department undertook its own maternal health program in 1940, when contraception was legally approved but limited to reasons of health. Despite many wartime difficulties, the prematernal health program has continued, with 146 clinics in operation by 1946.

Voluntary sterilization seems to be more widely known than more orthodox contraceptive methods. The operation, requiring consent in writing of both the woman and her husband, is usually performed 24 to 48 hours after delivery. Scanty statistics for seven hospitals indicate about 1200 sterilizations annually for the last three years. The author does not like this development, but admits that the low general educational level and the desperate poverty may make "planned sterility" a necessary weapon against excessive population growth. 5 tables.

THE SPACING OF BIRTHS IN THE FAMILIES OF UNIVERSITY GRADUATES

W. A. ANDERSON

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Amer. J. Soc., **53**: 23–33, 1947

Sydenstricker's study of the fertility of rural women in western New York (1932) is the only one known to the present author which deals with child-spacing in completed families. The current article on birth intervals is based on information obtained from the graduates of the classes of 1919, 1920, and 1921 from Cornell University. These are families in which childbearing is over, as indicated by the fact that over 99 per cent of both the men and the women are 45 or more years old. The results in general corroborate those of Sydenstricker.

Analysis of the child-spacing in these completed families reveals that first births, on the average, occur about 2.5–2.9 years after marriage. Although more than 50 per cent of first births come within the first two years, nearly 30 per cent are delayed at least three years after marriage. The intervals between successive births are usually longer, on the average, than the interval between marriage and the first birth. Furthermore, in families of a given size, the average length of the birth interval increases for each successive birth, the first being the shortest and the last usually the longest.

The average length of the interval between marriage and the first birth is longest in the one-child family (4.2 years for both men and women graduates), and decreases until it is shortest in the largest families. Similarly, the average

length of the intervals between successive births is less as the size of the family is greater.

This pattern of spacing seems quite uniform for all the graduates, regardless of age at marriage or of environment.   The author suggests that, if these patterns hold, it may be possible to predict the probable size of the family from the time intervals of the early births.   Inquiry into contraceptive controls or other factors is the next step for study.   7 tables.

MISCELLANEOUS

SHOCK IN OBSTETRICS

According to Sheehan, shock is associated with slackening blood-flow through skin, kidneys, liver, and probably the abdominal viscera. The blood returns slowly to the right heart, and the ventricular output is small. A rise in diastolic pressure, with a fall in pulse pressure, might first indicate shock, preceding the fall in systolic and diastolic pressures. In all cases dying after more than 3–4 hours of shock he has found subendothelial hemorrhages corresponding in distribution to the left branch of the atrioventricular bundle, rare in other conditions except eclampsia and cerebral lesions. Great distention is often seen in the stomach and proximal colon, corresponding to sympathetic nervous distribution and suggesting possible common cause for this distension and the subendocardial hemorrhages associated with cerebral irritation. The suprarenal cortex is not involved, and the anterior pituitary necrosis seen may be a result rather than cause. After severe hemorrhage there is a sharp decrease in blood volume, and vasoconstriction except in the brain. The same vasoconstriction is seen in shock, where it appears to be a harmful response interfering with visceral and cardiac blood-flow. Is it a result of sympathetic overactivity or an attempt to restore blood volume? Observations that transfusion, effective where collapse is due to hemorrhage, is valueless where there is none, cast doubt on the view of shock as due to reduction in blood volume.

Careful antenatal care and prophylaxis by good conscientious obstetrics were emphasized in the prevention of shock. Effective action against hemorrhage, the agent in the great majority of shock cases, should be taught above all. Fresh blood is best for transfusion, and Stansfield had some success in running plasma into 2 or 3 veins under pressure, along with "heparinisation." Prescott gave the cardiovascular criteria of shock as a pulse pressure less than 10 mm. Hg or a systolic below 80. Overheating is dangerous. Cardiac stimulants are useless, but morphine is good in conscious patients. The fetal heart-rate, according to O'Sullivan, shows disturbance before the mother's, and should be counted routinely. Too-zealous efforts to overcome retention of the placenta were discouraged. The Credé maneuver was condemned. Several recommended injection of pituitary into the uterine muscle.

Associated suggestions included a service to deal with postpartum hemorrhage in the home, and utilization of the placenta as a source of blood for storage.

BOOK REVIEW

PRACTICAL OBSTETRICS. *By Bruce T. Mayes, M. V. O., M. B., B. S. (Sydney), F. R. C. S., (Edin.), F. R. A. C. S., F. R. C. O. G.; Professor of Obstetrics, University of Sydney; Senior Honorary Obstetrician, King George V. Memorial Hospital for Mothers and Babies, Sydney; Honorary Obstetrician, Royal Hospital for Women, Sydney; Honorary Consulting Obstetrician, Women's Hospital, Crown Street, Sydney. The Australasian Publishing Co., Sydney, Australia.*

As the author notes in the Preface, this volume is not a textbook but rather a series of practical clinical discussions of the common complications in obstetrics, written in a form which preserves the atmosphere of the consulting room, the surgery or the bedside, rather than that of the lecture theater. Our British colleagues have a way of handling this informal type of presentation extremely well. For instance, in Victor Bonney's recent volume, "The Technical Minutiae of Extended Myomectomy and Ovarian Cystectomy," the style is so casual and conversational that it gives the feeling of being actually present at the operation and hearing the off-hand comments of the master-surgeon to his assistants. Mayes' very intimate manner of presentation achieves the same end; and the personal experiences recorded, the running comment and staccato injunctions, bring author and reader very close and drive home a host of practical points in forceful and readable fashion.

"It is not my policy in this book," Mayes writes, "to engage you in a scientific study of theory. In telling you these stories I have constantly before my mind the young doctor going into practice and wanting to know how to deal practically with the problems of obstetrics." To meet the needs of such a practitioner is the main objective of the book. As an example of the sound clinical wisdom it contains we read at the very outset: "If I were asked to formulate one guiding principle for the practice of obstetrics, it would be, Early diagnosis: late interference. Many of the problems of obstetrics are made for us by lack of early observation and by over-zealous interference. Breech presentation and induction of labor are outstanding examples."

The first complication considered is postpartum hemorrhage. In the discussion of a bleeding third stage, the technique of the Credé expression and of manual removal of the placenta is described in detail, with the latter illustrated by instructive diagrammatic sketches in color. For hemorrhage after delivery of the placenta, the usual oxytocic drugs and abdominal compression of the uterus are recommended and if these fail, bimanual compression. Like most British authors, Mayes condemns uterine packing, stating "I did once and would not do it again. It is neither easy nor effective." Also, like other British authorities, Mayes recommends an intrauterine douche for postpartum hemorrhage,—in this instance, one containing 5 per cent Dettol at 120 F. He believes that it contracts the uterus. Although this procedure is deeply entrenched in British obstetrics, it is rarely employed in the United States and personally I question its value. Nor has Dettol taken hold in this country despite a rather widespread trial in

the thirties. Most obstetricians here would feel that the sulfonamides and/or penicillin offer more efficacious prophylaxis against infection.

In his consideration of breech presentation the author emphasizes its increased fetal mortality, the value of external version at 36 weeks, the importance of slow extraction and the advantages of rotating the baby for delivery of the shoulders. In the course of this section he laments the fact that chloroform anesthesia in obstetrics is almost a lost art; and in this many of us would concur.

Episiotomy and repair are described in detail and many of the minutiae discussed should prove helpful reminders to the practitioner. Mediolateral episiotomy is recommended without mention of median; Nos. 1 and 2 catgut are used and the repair is done only after the placenta is expressed. These recommendations are in keeping with the practice of many good obstetrical clinics in the United States, but in view of the many advantages of median episiotomy (to my mind, overwhelming advantages) this procedure would seem to deserve at least passing mention, as would also the merits of finer catgut such as double and triple zero. Postponement of the episiotomy repair until after expulsion of the placenta is widely taught and practiced in the United States, but has many draw-backs, such as tendency to hurry the third stage and prolongation of anesthesia. Attempts to hasten the third stage may lead to so much trouble that we have never followed this doctrine in my own clinic, but deliver 90 per cent of placentas after completion of the repair and have found no reason to regret this practice.

In keeping with the author's policy of emphasizing the common complications, the toxemias of pregnancy receive extended consideration with proper stress on dietary management and much sane advice as to what to do and what not to do under specific circumstances, all documented by instructive case histories. Other chapters deal with prolonged labor, occiput-posterior positions, induction of labor, forceps delivery, therapeutic abortion, "How to do a lower segment Caesarean," etc. The last named is replete with instructions about the minutiae of technique many of which might prove helpful reminders even to experienced operators. Extensive sections on sterility and the Rh factor are also included.

Coming from Australia the chapter on rubella as a complication of pregnancy will naturally be of interest to obstetricians everywhere, particularly in regard to whether therapeutic abortion is indicated. Although Mayes sees and weighs both sides of this onerous question, he notes that operative interference is not legally possible in his country on this indication and does not recommend it in the present state of our knowledge. He feels that further data are necessary before the question can be decided but that "if the causal relationship of rubella in the mother to congenital defect in the child can be established in a high percentage of cases, then interruption would be justified."

One of the features of the book is the large number of instructive illustrations. The policies recommended are conservative and the practitioner who reads the volume and takes to heart its sound teachings will be a safer practitioner for so doing.

—EDITOR

Maternal Mortality Reports

The patient was a thirty-eight year old para 13, the details of whose previous obstetrical history are unknown, but were presumably normal, in that she was delivered on each occasion at home by a midwife. The patient had received no prenatal care, and when approximately one month from term she called in a midwife because she was having painless vaginal bleeding. The midwife then called a local physician who visited the patient in her home on March 25. At that time she stated that she had been bleeding for approximately 12 hours, and the physician noted considerable blood on the bed clothes and floor, and estimated that the patient had lost at least 600 cc. Examination revealed that the patient was not in labor, her color was good, the blood pressure 130/80, pulse 80, and the fetal heart was heard in the left lower quadrant. Neither rectal nor vaginal examination was carried out, and the patient was given sedation, put to bed, and instructed to remain in bed. The local county hospital was requested to admit the patient, but stated that no beds were available, and the physician concluded that transportation to a more distant hospital would be unsafe.

The physician made a routine follow-up call 24 hours later to find that the patient had succumbed 3 hours before his arrival. She had felt weak, and had decided to get up and sit in a chair, after which she began to perspire profusely and slumped down into the chair unconscious. At the time of the return visit after the patient's death, there was no evidence of further massive vaginal bleeding.

Discussion: The importance of understanding the significance and potential danger of painless vaginal bleeding in the last trimester of pregnancy has been pointed out many times previously by this committee. In spite of constant attempts to impress upon physicians the dangers of disregarding painless vaginal bleeding, we still find cases of this nature. The physician in this case apparently made a half-hearted effort to have this patient hospitalized, and when this proved difficult he gave up his attempts to secure hospitalization elsewhere. A patient of this sort would have been far better off traveling 50 or even 100 miles to a hospital than left at home. The members of the committee could recall many cases far more desperate when first seen than this one, who had survived long trips by ambulance, when they were given blood and proper treatment upon admission to a hospital.

The patient was a twenty-seven year old colored para 1 with 1 living child who was due by dates on July 8. Her previous pregnancy was terminated by cesarean section, the indication for which is not known. In the present pregnancy she consulted her physician when she was approximately 6 months pregnant, and the only abnormality noted was the presence of the scar from the previous cesarean section. The physician advised hospitalization because of the previous cesarean section, but the patient refused to accept his advice. External pelvic measurements were normal, but internal pelvic measurements were not done.

Labor began on July 6, and the patient was seen in her home soon after the onset of uterine contractions. She was having regular pains of good quality about every 10 minutes. On rectal examination the cervix was 4 cm. dilated, with the head in mid-pelvis. The patient was given 3 grains of nembutal. The physician returned a few hours later and found the child with head and arms delivered. The delivery was completed without difficulty and manual removal of the placenta was performed. The patient was in shock at the time of

delivery, and although none of the subsequent details are known, she apparently remained in shock at home and died 6 hours 20 minutes after delivery.

Discussion: Many details which would be of great interest in this case are lacking and cannot be obtained. Why was manual removal of the placenta performed and was the uterine cavity thoroughly explored at this time? In spite of meager information the committee felt that rupture of the uterine scar was the probable cause of death and that the death was clearly preventable on a number of counts. First, the physician was at fault in accepting the responsibility for home delivery in a patient of this type. Secondly, having done so, he should certainly have remained with the patient throughout her labor and for several hours postpartum. Thirdly, the patient although in obvious shock, lived for six hours after delivery, during which time hospitalization, transfusions, and hysterectomy could have been accomplished.

CASE NO. 54

The patient was a twenty-six year old white multipara with one living child resulting from one previous pregnancy, whose estimated date of confinement was December 1. Her previous pregnancy had been terminated several weeks prior to term by cesarean section because of severe pre-eclampsia. This infant weighed 3 lbs. 12 oz. at birth and survived. The patient's postpartum course following this delivery was not remarkable. With the current pregnancy the patient did not seek medical attention because she was afraid she might be subjected to another cesarean section. Accordingly she was not seen until November 15, approximately two weeks from term, at which time she presented herself to her physician's office at 7:00 A.M., complaining of vomiting and epigastric pain. Examination at that time revealed her blood pressure to be 220/180, and the urine contained a 4 plus albumin. She was immediately admitted to the hospital and given 300 cc. of 25 per cent glucose intravenously and "sedation." At 11:00 A.M. the same morning classical cesarean section was performed under spinal anesthesia, 10 mgm. of pontocaine, supplemented by intravenous sodium pentothal. The operation was performed uneventfully and the patient was returned to her room. On reaching the room it was noted that the patient was in profound shock, and she was given plasma and 10 per cent glucose in distilled water intravenously, and grouped and matched for transfusion. She responded to treatment, but at 4:00 P.M. on the day of operation she again went into shock and was given a blood transfusion of 500 cc. of whole blood. For the next four days the patient's course was characterized by alternate periods of shock which were treated by two more blood transfusions, amigen, plasma, and 5 per cent glucose in distilled water. In spite of this therapy the non-protein nitrogen rose gradually to 130, and the urinary output averaged approximately 50 to 100 cc. per 24 hours. There was moderate postoperative abdominal distention, and the patient was in an oxygen tent from the day of operation until the day of death. She failed to respond to any treatment and succumbed on the 6th postoperative day.

Discussion: The handling of this patient was discussed primarily from two points of view. First of all, the patient unquestionably should have sought medical care long before she did. Adequate prenatal observation and therapy could have prevented the occurrence of such an extreme degree of pre-eclampsia.

While the above seemed fairly obvious, the committee discussed at length the treatment of the patient once her serious condition had been determined and she had been admitted to the hospital. It was the feeling of the committee that cases such as this should be treated conservatively for a matter of 12 to 24 hours.

The inclination to rush in on a case with such obvious fulminating pre-eclampsia is understandable, but it is probably wiser to give the patient rest in bed and attempt to stabilize the condition prior to operation or delivery. The postoperative course of this patient is fairly typical of a large number of severe pre-eclamptics, in that they are prone to go into postoperative or postpartum shock. It was the committee's decision, therefore, that a more prolonged period of observation, liberal use of sedatives, and general supportive therapy would have greatly lessened the likelihood of postpartum shock. On these grounds the death was voted preventable on two counts, namely the patient's obvious neglect of her own condition, and also unwise and hasty interference on the part of the physician.

CASE NO. 55

The patient was a thirty year old colored multipara with 7 previous uneventful pregnancies and 7 living children, who was admitted to the hospital on September 19, with the following history:

The patient had fallen into labor spontaneously at 2:00 A.M. on the day of admission, having received no prenatal care during her pregnancy. She was attended during early labor by a midwife, who observed the patient throughout the early morning, and noted that the patient was having hard pains every 3 to 4 minutes. At 4:00 A.M. the blood pressure was 165/100, pulse rate 84, and the presenting part could not be made out by the midwife. A request was made by the midwife to have the patient hospitalized because of inability to determine the presentation. On the way to the hospital by ambulance the patient suddenly stopped having uterine contractions and began to have vaginal bleeding. Upon admission to the hospital at 9:05 A.M. her blood pressure was 135/90, pulse 160, and there was constant moderate vaginal bleeding. Sterile vaginal examination was carried out 25 minutes after admission, but the vagina was so completely filled with blood and blood clots that no information was obtained. The presenting part could not be felt in the pelvis. Blood was taken for grouping and matching, and a surgical consultant called. The consultant ordered the patient to receive 50,000 units of penicillin and to be sent to the x-ray department. At the time the patient was taken to the x-ray department she was bleeding profusely, was cold, clammy, disoriented, and exhibited air hunger. The x-ray report, received later, stated that the patient was bleeding so profusely that she was uncooperative, and the films were very unsatisfactory. The fetus by x-ray was displaced markedly upward. A catheterized specimen of urine revealed a 3 plus albumin, 3 plus sugar, 30 to 40 red blood cells per high power field. At 11:40 A.M., 2 hours 35 minutes after admission, she was taken to the operating room and blood transfusion begun. By this time the patient was in such profound shock that a lower midline abdominal incision was made without anesthesia. The peritoneal cavity was filled with blood and contained the placenta and all of the fetus except the head, which remained within the body of the uterus. There was a large rupture of the uterus extending from the vagina to the region of the attachment of the round ligaments. A stillborn male infant weighing 4850 gm. was delivered at 12:16 P.M. Supravaginal hysterectomy was carried out as rapidly as possible, but in spite of 1,000 cc. of blood, oxygen, stimulants, and morphine, the patient remained in profound shock, and respirations ceased at 4:00 P.M.

Discussion: In a patient of upper parity range who suddenly and abruptly stops having contractions once they have been well established and commences to have vaginal bleeding, and shows red cells in a catheterized specimen of urine, the probability of rupture of the uterus is so good that further investigation is certainly unnecessary. The committee was totally at a loss to understand why

this patient with such a classical picture and history of uterine rupture should have been sent to the x-ray department, or even why sterile vaginal examination was attempted. Two and one-half very vital hours were lost in the handling of this case. Immediate plans for blood transfusion, plus surgery as soon as possible, would most likely have saved this patient's life. It was also noted that the physician called in consultation was a general surgeon, and the committee felt that the policy which exists in so many communities of turning desperate obstetrical cases over to general surgeons is one that should be remedied as soon as possible. Had the physician in question had obstetrical training, he certainly would have realized first, the true nature of the condition which confronted him, secondly, the urgency for immediate operation, and thirdly, the futility of carrying out x-ray studies.

CASE NO. 56

The patient was a twenty-seven year old para 1–0–0–1 whose estimated date of confinement was November 14. Her previous pregnancy and labor had been uncomplicated and in the present pregnancy she had made ten prenatal visits starting at the second month of pregnancy. No abnormalities were noted at any time.

She fell spontaneously into labor on November 12 at 8:00 A.M. and at 12:30 P.M. notified her physician that her pains were more frequent. She was instructed to go at once to the hospital. Shortly before leaving home, she ate a large meal. Labor progressed rapidly and at 3:45 P.M. the head was on the perineum and visible with a pain. An inhalation anesthetic was begun and soon thereafter she vomited a large amount of food which was aspirated. All efforts to clear the air passages were futile and she was pronounced dead at 4:00 P.M. A living infant was delivered by low forceps two to three minutes after the mother's death.

Discussion: Deaths such as this are doubly tragic because of their suddenness and total unexpectedness, and because of the ease with which they can be prevented. Patients should be instructed not to eat solid foods after the onset of labor, and it should be a rigid routine to ask patients when they last had a meal before administering inhalation anesthetics. In this particular case gastric lavage or the use of regional anesthesia would have avoided the catastrophe.

CASE NO. 57

The patient was a twenty-eight year old white primigravida whose estimated date of confinement was December 17. She entered the hospital in active labor on December 18 having never been seen by a physician prior to that during her pregnancy. On admission she was found to be in good labor with the vertex presenting and the cervix partially dilated. The pulse rate was recorded as 120 per minute. Blood pressure was not determined and the urine was not examined. The physician in charge states that with patients in active labor on admission urine and blood pressure determinations are not done "unless there are indications for it."

After a labor of 18 hours she was delivered spontaneously of a living child. Whether she received any anesthesia or analgesia is not known. Following delivery the pulse rate remained rapid at approximately 120 per minute and accordingly she was given 500 cc. of 10 per cent glucose in normal saline intravenously. Soon after completion of this therapy the patient complained of chest pain and suddenly expired. Postmortem examination was obtained revealing rheumatic heart disease with acute congestive heart failure.

Discussion: In view of the fact that in this case the blood pressure was not determined and the urine was not examined it can be assumed with reasonable certainty that examination of the heart and lungs was also omitted when this patient was admitted to the hospital in active labor. One wonders what set of circumstances the physician in this case would have considered as an "indication" for such examinations, probably massive edema and convulsions would have been considered sufficient indication for taking the blood pressure and examining the urine. Fortunately there is no question as to the cause of death since postmortem examination revealed that the patient did have rheumatic heart disease and died of acute cardiac failure. The patient's consistently elevated pulse rate should have made the physician suspicious of something wrong, and the committee considered it utterly inexcusable that any patient, particularly one with no prenatal care, should have been so grossly neglected. Nothing more than the usually accepted routine examinations upon admission would have unquestionably disclosed the pathology present, and the institution of proper therapy for a patient with heart disease would most probably have altered the outcome.

CORRESPONDENCE

November 4, 1947

To the Editor:

I wish to comment on three of the cases in the Maternal Mortality Reports of the October, 1947 issue of the SURVEY.

Cases 49, 50 and 51 all died from hemorrhage. The Committees have pointed out wherein the patients failed to receive appropriate treatment. In case 49, the Committee makes the statement that, "the insertion of the vaginal pack in postpartum hemorrhage is not only useless, but dangerous." To this statement I emphatically want to take exception.

The vaginal pack is very effective in helping to control postpartum hemorrhage. The vagina should be packed tightly and the uterus must be held and compressed through the abdomen, thereby closing off the uterine sinuses. The vaginal pack produces counter pressure against the uterus. Naturally, the patient should not have been left alone without the uterus being held and no oxytocic being given; a transfusion should have been given before the 3 hours and 20 minutes.

In Case 50, there was difficulty in delivering the placenta for 30 minutes. Undoubtedly, the woman bled during that period. A vaginal examination should have been made and the placenta delivered sooner, as placentas separate as soon as the baby is born. In this case, the uterus was packed. But, in order to pack the uterus, the woman who already was in shock had to be anesthetized which added to her shock and caused the uterus to further relax. Vaginal packing can easily be done without anesthesia, and together with compression of the uterus is very effective.

In Case 51, it was discovered that the lacerations of the cervix, 3 to 4 inches long, extended into the lower uterine segment. Packing the uterus only aggravated the condition by distending the uterus and extending the lacerations further and causing them to bleed still more. By packing the vagina, not the uterus, and compressing the uterus from above, there was a possibility of reducing the bleeding until a hysterectomy was done. The hysterectomy should have been done within the hour.

I have been advocating packing the vagina as a simple and very effective procedure for the control of postpartum hemorrhage and have condemned packing the uterus as unphysiological and illogical. In order to control bleeding the uterine sinuses must be compressed, whereas packing the uterus distends the sinuses and induces more bleeding.

(Signed) Morris Leff, M.D.
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(As noted in italics under the heading "Maternal Mortality Reports," the discussion appended to these reports are those of the committee concerned and do not necessarily represent the attitude of the Editors. When used as counter-pressure to abdominal

pressure and massage, as recommended by Dr. Leff, the vaginal pack may well possess some value, but when employed without constant abdominal pressure it serves, in my opinion, little purpose and sometimes leads to a false sense of security. We have not used vaginal packing in our clinic in the treatment of postpartum hemorrhage due to uterine atony for many, many years. Dr. Leff's condemnation of the intrauterine pack is in keeping with opinions expressed in several editorial notes during the past year.—Ed.)

Gynecology

ENDOCRINOLOGY

DIAGNOSIS AND THERAPY IN UNUSUAL CASES OF HYPOTHYROID DYSCRASIA IN GYNECOLOGY AND OBSTETRICS

J. R. Goodall

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Thyroid dyscrasias of the deficiency type outnumber the excessive secretory cases in the ratio of about 50 cases to 1 in private practice. This article deals chiefly with the unusual, but very common, clinical types of hypothyroidism. Stress will be laid upon the unusual characters of the symptoms and signs,—a recognition of which will lead to appropriate treatment and prompt improvement of the distresses.

To facilitate description, the first part of the paper deals with the unusual cases in gynecology; the second part with the obstetrical cases.

GYNECOLOGICAL CASES

Starting from the head and working downwards, we first encounter headaches. These fall chiefly into two groups; severe headaches of a local or general nature; and the migraine type of local pain. These two may prove to be ultimately of the same nature. A second characteristic deficiency type is that which is experienced only at menstruation, or greatly increased at that time. Its location is various, but is generally relieved when the menses is properly established.

Another type of case, caused by thyroid deficiency, has to do with the intrathoracic organs. One patient developed sudden attacks of retrosternal pressure and constricting pains with inability to retain food. When given thyroid she promptly recovered, digested her food and began to gain weight. She has had 3 recurrences since she stopped therapy. The author next discusses a series of cases which he classifies as pseudo-anginal and which were cured by thyroid treatment. Still another group presented a clinical picture suggestive of bronchitis and yet were relieved by thyroid. An especially interesting series of cases of thyroid deficiency show spasm of muscular structures in the vicinity of the gallbladder.

Colitis. Colitis is one of the most common of women's diseases. It constitutes about 5 per cent of the author's office practice and he is convinced that a very large percentage of cases of operations done for appendicitis and ovarian trouble are really colitic cases with fixed pain. The cases of colitis affecting the

whole of the colon, or cases of shifting pain along different parts of the colon at different times, lend themselves easily to diagnosis, but on the other hand, cases of fixed pain localized in any of the abdominal quadrants may tax the acumen of the most careful diagnostician.   Many of the cases of colitis are due to allergy, but many if not all, have a nervous element as well.   In many of the allergic ones there is an absence of hydrochloric acid in the stomach secretion, and where this is the case and there is achlorhydria, thyroid treatment is usually followed by most gratifying results.

Pelvic thyroid dyscrasias.   It is in this field that one meets with the most striking responses to therapy in gynecology.   It is a general rule, not without its exceptions, that cases of athyria are disposed to menorrhagia or metrorrhagia, and that hypothyrodism is prone to produce scanty menstruation or amenorrhea. One of the common types is that of a young girl in the first years of puberty who complains of menorrhagia or metrorrhagia.   In many of the cases the thyroid has been enlarged since the onset of menstrual periods.   There are often signs of a generalized gland deficiency, involving chiefly the anterior pituitary gland. There is frequently in addition to the enlarged thyroid, hirsutism, a high palate, milk spots on the nails and teeth, dry hair and skin and other signs of thyroid dyscrasia.   The case would seem hopeless from the point of view of therapy, and the author must confess that anterior pituitary extracts have proven quite ineffective in such cases, but that one can accomplish extraordinary results with exhibition of thyroid.

Dysmenorrhea.   In many cases of crampy dysmenorrhea occurring during the first day of the menstrual flow, the cause can be laid to uterine allergy.   There are many other causes, of course, but in private practice allergy will account for about 20 per cent of the cases.   The high palate, and the other signs of thyroid deficiency, may or may not be present.   If present, the diagnosis becomes easy, but if absent in such cases, it will repay the trouble of using the therapeutic test by giving the patient small doses of thyroid while she is kept under close observation, and increasing the dose carefully until relief or cardiac acceleration occurs. Many of these cases are promptly relieved and it is common to have the patient state that her first menstruation after treatment came on without symptoms. Many of the cases are associated with a degree of anemia, and the exhibition of iron under these circumstances is highly recommended.

THYROID DYSCRASIAS IN OBSTETRICS

Dystrophies in the field of obstetrics offer a wide and very diversified field of symptoms and signs.   Probably the most interesting are the troubles leading to *sterility.*

It is now established that a very large percentage of cases of sterility, both in the female and the male, owe their source to a deficiency in thyroid secretion. When it has been established by examination that the female passages are patulous and that the sperms are in a sufficiency and of normal activity, whether or not the women present clinical signs or insufficiency of the thyroid, a small dose of thyroid very frequently brings a prompt improvement in fecundity.   Genito-

urinary specialists affirm that the same holds true for the male. Many women now know that they can remain sterile as long as they wish and become pregnant also when they wish through the use of thyroid. Thyroid has become a routine in all cases of this type and the results have been most gratifying. But the happiness experienced by the conception is often destroyed by miscarriages in these cases, because the thyroid tablets are often withdrawn once conception has taken place. It is imperative that the dose of thyroid be continued throughout the pregnancy in increased doses, or faulty implantation and hemorrhage may destroy the pregnancy. This leads us to the subject of thyroid abortion. Thyroid deficiency is one of the common causes of this disease, and the exhibition of thyroid in the early state of the uterine pain and bleeding will frequently permit the pregnancy to continue to term if damage of an irreparable nature has not preceded the symptoms of abortion. It is a peculiar paradox that in so many cases of thyroid deficiency a large number are sterile owning to the insufficiency, whereas in others fertility seems not to be interfered with but habitual abortion is the rule.

It is difficult, in fact impossible, to explain the action of thyroid in these cases. Does thyroid merely heighten general cell activity, or has it some specific action? There seems no adequate explanation for the lack of fertility in hypothyroidism other than that of lowered cell vitality. But beyond this may be some deep intraovular or intraspermal activity for which thyroid is a specific and essential need. But in abortion, the fault would seem to be deep seated, inasmuch as many of these cases show a definitely diseased pregnancy. The pathology that is found varies greatly, but the variations are probably but late sequelae of a primary cause.

(The above paper is one of many fine contributions contained in the special Rubin Anniversary number to which the September and October issues of the Journal of the Mt. Sinai Hospital are devoted. It marks a well-deserved tribute to Dr. I. C. Rubin on the 25th anniversary of his introduction of the now universally used procedure of tubal insufflation, the most important advance of our generation in the study of female infertility. The special number, which has been prepared in beautifully bound form, numbers no less than 842 pages, representing a large number of valuable contributions by Dr. Rubin's friends and admirers, not only in this country, but others as well. Abstracts of a number of their papers are published in the present number of the SURVEY, and other abstracts of selected articles in the Rubin Anniversary volume will appear in our next issue.

The author of this paper, one of the most outstanding of Canadian gynecologists, died only within the past few months. With regard to hypothyroidism in gynecology and obstetrics, there can be no doubt as to its relative frequency and its important bearing on . many functional disorders, such as amenorrhea, hypermenorrhea and sterility. As a matter of fact, there are few who do not frequently resort to thyroid therapy on a purely empirical basis, when there is no laboratory evidence of thyroid hypofunction, and who nevertheless are convinced of the value of such treatment. That the thyroid is in some way functionally linked up with the gonads seems certain, but the exact nature of the mechanism involved has not been clarified.

Goodall's paper, however, discusses thyroid therapy, also empirical, for various other indications in which there seems to be a definitely lesser degree of hopefulness as to results. It is true that all sorts of symptoms may at times be taken to represent a masked hypothyroidism or, as Goodall calls it, a thyroid dyscrasia. Among these he includes headaches,

not necessarily of cyclical or menstrual type, migraine, gastrointestinal symptoms of various sorts, pseudo-angina, severe spasmodic coughing, gall-bladder symptoms, colitis, dysmenorrhea, etc. Taking random shots at such disorders with thyroid, although certainly they are much more apt to be unrelated to thyroid function, may occasionally yield a surprisingly good result, but much more frequently will result in disappointment. A much more flagrant degree of empiricism would seem to be involved in the thyroid therapy of such conditions than with disorders which are rather clearly linked up with the endocrine glands. Goodall does not of course attempt to set up a rationale for such therapy, contenting himself chiefly with reports of cases in which thyroid therapy had apparently yielded striking results.

When he discusses the frequent value of thyroid in sterility and habitual abortion, he is much more in step with obstetricians and gynecologists generally, getting a bit out of line again when he discusses its value in subinvolution.—Ed.)

AN EVALUATION OF ESTROGEN THERAPY

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New Orleans M. & S. J., **99**: 599–605, 1947

The writers review the therapeutic principles to be observed in the clinical application of the ovarian hormones, estrogen and progestin. The first of these basic maxims is the elimination of organic disease. This entails a complete survey of the patient to exclude the presence of any gynecologic organic disorder or constitutional ailment which would preclude endocrine therapy. The second principle is individualization, or the knowledge that no 2 patients ever present the same problem. Third is the importance of evaluation of the pathologic physiology. The authors review the physiology of normal menstruation. It is clear that estrogen is the hormone of growth, vascularization and preliminary preparation, whereas progestin is the principle which modifies and differentiates. The fourth therapeutic maxim is the application of basic pharmacology. The ovarian hormones belong to the steroid family, a group which also includes androgens and the adrenocortical hormones. Both estrogen and progestin have the significant dual ability of acting on the genital end-organs and on the anterior lobe of the hypophysis. The latter characteristic is important to remember when treating a regularly menstruating woman because the rhythm of her cycle may be disturbed through depression in the production of hypophyseal gonadotropic hormones.

The currently accepted usages of estrogen in the treatment of atrophic vaginitis, amenorrhea, puerperal breast engorgement, and the menopausal syndrome are discussed. In atrophic vaginitis it is logical to administer small doses of estrogen in order to restore the vaginal epithelium to its former state of resistance. Estrogen may be given effectively orally in a dose of 0.5 mg. of stilbestrol daily for several weeks or by the nightly introduction of a vaginal suppository contain-

ing 0.2 mg. of estrone. However prescribed, the estrogen should be discontinued in a month and repeated only if required for a recrudescence of symptoms.

The treatment of amenorrhea with estrogen alone is notoriously unsatisfactory, since estrogen can produce only the proliferative phase of endometrial growth. The physiologic objective of estrogen therapy in amenorrhea is to combat uterine hypoplasia; if the uterine atrophy is the *sole* cause of the amenorrhea, good results may be obtained by estrogen therapy. An effective technic of employing estrogen in the treatment of amenorrhea is either its simultaneous combined, or its consecutive cycle administration with the corpus luteum hormone, progestin. With the cyclic method, one may administer 1.5 mgm. of estradiol benzoate intramuscularly every third day for 5 doses and follow immediately with 5 daily injections of 10 mgm. of progesterone. Such dual therapy, whether combined or cyclic, is generally repeated for 3 consecutive months.

As little as 1 mgm. of stilbestrol, or its equivalent in natural estrogen, given orally 3 times daily is adequate for the prevention of puerperal breast engorgement. Such treatment should be discontinued within 10 days and is best withdrawn gradually. The danger of administering estrogen during the puerperium for too long a period lies in the fact that it is capable of creating hyperplasia of the regenerating endometrium with resultant abnormal bleeding.

It is stated that the vast majority of women undergoing the climacteric do *not* require treatment for the menopausal syndrome. An explanation of the temporary nature of the symptoms coupled with the prescription of mild sedatives may be all that is required. However, when the symptoms are marked, there is no more specific therapy than estrogen. It is logical to administer the smallest amount necessary to assuage the vasomotor symptoms. It should be prescribed for only a limited period of time and should be withdrawn in a gradual manner.

It is emphasized that the natural and proper suspicion in all cases of postmenopausal uterine bleeding should be carcinoma of the uterus, and the attending physician should be impelled to inspect the cervix (executing a biopsy if indicated) and to perform diagnostic curettage. As an example of the fact that these admonitions are not universally borne in mind, the authors quote some of the recent statistics of the Philadelphia Committee for the Study of Pelvic Cancer. From December, 1945, until December, 1946, the Committee uncovered 116 instances in which there had been unwarranted delay in the diagnosis of pelvic cancer. Of the 116 instances, 78 were classified as "physician delay" and the remaining 38 as "physician and patient delay." Thirty-one of the 116 patients were given medication, oral or hypodermic or both, in the presence of symptoms suggestive of pelvic cancer, *without examination.* Two case histories from the 116 are cited in this paper.

The contraindications to estrogen therapy are detailed. First, the authors avoid the use of estrogen therapy during the premenopause. If given at this time, estrogens may easily evoke more irregular bleeding, and may possibly prolong the adjustment of the body to the changing endocrine status. The second contraindication is residual endometriosis. It is best, the writers believe, to avoid the use of estrogen in any woman giving a history of endometriosis. If

the castration syndrome cannot be controlled with sympathetic reassurance and mild sedatives, androgen therapy may be employed. The third contraindication is a carcinoma background; if there is a clear-cut history of multiple instances of either mammary or uterine cancer in a patient's family background, it would appear safer not to administer estrogen to that patient. It goes without saying that if the patient herself is a salvaged survival from either type of malignant neoplasm she should not be given estrogen. Finally, estrogen should not for any reason be administered to a patient who exhibits, or who has recently had excised, a fibro-adenoma of the breast. Similarly, the presence of fibromyomas serves as a contraindication to the use of estrogen.

(This is a well-organized, sound and conservative evaluation of estrogen therapy. Clinicians will of course differ somewhat as to the methods and dosages employed in such treatment. For example, in senile vaginitis, I would not wish to employ the daily estrogen doses recommended by the authors for a period of several weeks at a time, feeling that these might often be followed by bleeding. For this form of vaginitis, as well as for the gonorrheal vulvovaginitis of children, I prefer the vaginal route to the oral or hypodermic.

The authors wisely call attention to the possibility of producing endometrial hyperplasia and bleeding by the large doses of stilbestrol so commonly employed for the suppression of puerperal breast engorgement and lactation, though the value of this treatment for the latter of these indications is rather limited. I have seen a considerable group of cases in which such bleeding occurred, sometimes necessitating curettage for either diagnostic or therapeutic reasons.

The admonition that the estrogens be employed in menopausal women only if vasomotor symptoms constitute a real problem and that their use be limited to the smallest doses necessary and that it should not be continuous, may be heartily and heavily underscored.

Finally, every gynecologist of experience has encountered cases of even such grave diseases as cancer of the uterus or vagina in which stilbestrol or other estrogens have been used for long periods of time without even the simple pelvic examination which would have revealed the cause of the bleeding. The most glaring instance of this sort which I recall was that of a woman of 36 who had been getting "shots" for a whole year without any pelvic examination. Simple digital examination revealed a large carcinoma of the posterior vaginal wall which almost blocked the canal.—Ed.)

THE PRACTICAL APPLICATIONS OF ENDOCRINES IN GYNECOLOGY

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The ovarian hormones, the estrogens and progestins, induce the same changes in the genital tract which occur normally, and there are indications that they may in some way favorably influence the hypophysis.

The most obvious deficiency to treat with replacement of hormones is the ovarian failure at the climacteric. Here one should try to relieve the symptoms

with as small an amount as possible, because by giving estrogen it is easy to cause bleeding. Complete replacement therapy with estrogen and progestin in amenorrhea in younger women is practical, but not useful when it becomes clear that nothing beyond periodic bleeding is being accomplished and that the underlying disorder remains unaltered. However, there are conditions of less complete ovarian failure where replacement therapy is indicated to treat abnormal bleeding and where permanent benefit seems to be obtained. One of these conditions is a metropathia hemorrhagica. Curettage will stop the bouts of bleeding in such cases, but one hesitates to recommend it in teen-aged women, and the author shows that replacement of progesterone is just as effective and may even be curative. Bleeding can be stopped just as effectively with crystalline progesterone in oil, 10 mg. daily for 5 days or by anhydrohydroxy progesterone by mouth, 60 mg. daily for 5 days, as by curettage.

When attempting to produce normal menstruation in patients who are not bleeding, there are cases which demonstrate that estrogen, as would be expected, is not very beneficial and that 50 mg. of progesterone in one injection may be sufficient to produce bleeding.

Menorrhagia and dysmenorrhea may both, with some justification, be considered deficiencies of the corpus luteum. The best argument for this in menorrhagia is the fact that the addition of progestin before the menses is beneficial. Ten mg. of Pranone daily for the 10 days preceding menstruation may reduce the bleeding to normal. The most reliable method the author knows of to relieve dysmenorrhea in any one cycle is the giving of large doses of estrogen twice weekly during the first half of the cycle, beginning before the fifth day after the onset of menstruation, thus preventing the formation of a corpus luteum. This cannot be done every month, but it may be a useful treatment when a woman wants to do something special when her menses is due, or when it is desirable to give the patient occasional relief from severe pain. Progestin given before menstruation may relieve the pain, replacing a deficiency of corpus luteum function. A deficient corpus luteum is worse than none at all in dysmenorrhea.

Lastly, the writer discusses thyroid. There are those who say that it should not be used if hypothyroidism cannot be demonstrated. If this dictum is followed, opportunities for relieving very simply many of the milder menstrual upsets will be missed. A small daily dose of thyroid will do no serious harm and it may be followed after a month by a normal menstrual rhythm.

(The author, who is a well trained endocrinologist, is perhaps more enthusiastic about the effectiveness of progesterone in cases of metropathia hemorrhagica than some of the rest of us, although it is certainly one of the many hormonal methods which must be included in the therapeutic armamentarium of the gynecologist. Nor will everyone agree that dysmenorrhea is to be considered to be due to deficiency of the corpus luteum, or that progesterone is of much therapeutic value for this indication. In my own practice I find myself resorting to organotherapy of any kind less and less frequently in treating dysmenorrhea. An exception to this is in the employment of oral estrogens, such as stilbestrol, in the first half of the cycle, as mentioned by the author, for the purpose of inhibiting ovulation for the particular cycle. The succeeding period is often completely or almost completely painless, and the patient is given a big psychological boost when she learns that she

can have a menstrual flow without pain. Such treatment cannot of course be constant, and it is apt to be much less effective the second month than the first. There are other disadvantages, such as disturbance of the menstrual rhythm, but the occasional employment of the plan is a worthwhile addition to the management of this pesky disorder.—Ed.)

THE USE OF THE SEX HORMONES IN CLINICAL PRACTICE

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Ohio State M. J., **43:** 616–619, 1947

That some of the principles discussed in this paper may not survive in the coming years is entirely possible, indeed probable. However, for the present, if our treatment is to be honest and rational, the author states that these principles and the questions they raise must form the foundation of our therapy with the sex hormones.

These principles are: (1) All hormone therapy is substitution therapy. (2) Every hormone acts on a definite end-organ. (3) No hormone acts on the organ that produces it.

The questions raised by these principles are: (1) Is there an end-organ, other than the gland of production, which is capable of response? The error of giving tremendous doses of estrogens to a patient with primary mammary aplasia without bothering to determine whether or not there was acinar and alveolar tissue present is cited. (2) Is there a deficiency? We must either prove the deficiency ourselves for the particular patient, or the disease entity must be one which experience has shown is always associated with a deficiency state. (3) Is the deficiency physiologic? Thus the postmenopausal patient has a deficiency of estrogens, but she is supposed to have such a deficiency physiologically at her time of life. If this third question is answered in the affirmative, we must recognize that any substitution in the patient is contra-physiologic therapy. The dose should be the minimum effective amount, and the course of treatment should conclude as soon as possible.

The writer reviews the endocrine principles available and discusses what circumstances indicate their use.

(In a very broad sense, it is probably true that all hormone therapy is substitutional, although some of the better understood hormones can be handled pretty much like drugs, to produce certain desired results, not always of a highly specific nature. I endorse heartily the author's comment that the estrogen therapy which we all use in the treatment of severe menopausal symptoms is actually contra-physiologic, and yet rational if not abused, as it so often is.

It is physiologic for the function of the ovary to cease at this epoch, but in many patients this withdrawal of ovarian function produces temporary symptomatic repercussions, which can be relieved by the temporary administration of estrogens. But such therapy should

be only temporary and should be resorted to only when and if symptoms are really trouble-some. We can not "cure" a woman of the menopause, which is as inevitable and physio-logic as death itself. But we can practice a species of therapeutic euthanasia in so far as ovarian death is concerned, tiding the patient more gently over the symptomatic bumps which she may encounter until the endocrine family adjusts itself to the functional absence of its late lamented member, the ovary.—Ed.)

CLINICAL EVALUATION OF DIENESTROL, A SYNTHETIC ESTROGEN

A. E. RAKOFF, K. E. PASCHKIS, AND A. CANTAROW

Jefferson Medical College and Hospital

J. Clin. Endocrinol., 7: 448, 1947

Dienestrol was evaluated, with reference to clinical improvement, objective response and evidences of toxicity, in 82 patients with various conditions in which estrogen therapy was indicated.

In 40 menopausal women dienestrol afforded excellent relief in every instance, the minimal dosage necessary ranging from 0.1 to 1.0 mg., with an average of 0.43 mg. daily. However, the average dosage required to produce a slight estrogen effect in the deficiency smear was 0.77 mg., while to produce a marked estrogen effect required much higher dosages. Bleeding during treatment or on withdrawal occurred only twice on therapeutic dosages. It was difficult to induce bleeding in younger women with amenorrhea even with high dosages. In 26 postpartum patients inhibition of lactation was readily obtained with dosages of 1.0 mg. daily for 3 days and 0.5 mg. thereafter for one week.

No symptoms of intolerance to dienestrol were noted in any patient even with high dosage.

(As has been remarked on previous occasions, manufacturers have been working assid-uously to perfect non-hormonal oral estrogens comparable to diethyl-stilbestrol in potency and yet not producing the unpleasant side-effects which make the employment of the latter impossible in from 10 to 15 per cent of women. Such substances as dienestrol and meprane both appear to fill the bill quite satisfactorily, in this respect, in so far as I can judge from my own observation in recent months.—Ed.)

can have a menstrual flow without pain. Such treatment cannot of course be constant, and it is apt to be much less effective the second month than the first. There are other disadvantages, such as disturbance of the menstrual rhythm, but the occasional employment of the plan is a worthwhile addition to the management of this pesky disorder.—Ed.)

THE USE OF THE SEX HORMONES IN CLINICAL PRACTICE

A. C. BARNES

Ohio State University College of Medicine

Ohio State M. J., **43:** 616–619, 1947

That some of the principles discussed in this paper may not survive in the coming years is entirely possible, indeed probable. However, for the present, if our treatment is to be honest and rational, the author states that these principles and the questions they raise must form the foundation of our therapy with the sex hormones.

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estriol-A. Reduction of 16-keto-estrone yields 4 possible stereo-isomers, of which 3 have been prepared. The authors have determined the estrogenic activities of these compounds as well as of 16-keto-estrone prepared by partial synthesis from estrone. The results permit certain deductions regarding the probable pathway of estriol production in the organism.

FEMINIZING TUMOR OF THE TESTIS: PRESUMABLY ABERRANT ADRENOCORTICAL TUMOR

E. Östergaard

Viborg County Hospital, Copenhagen, Denmark

In most cases of feminizing tumors in adult males, the most conspicuous symptom of feminization is gynecomastia, accompanied by genital atrophy and sometimes loss of capacity for sexual function. The tumors which in adult males have given rise to feminization have originated from the adrenal cortex or testis. The feminizing adrenocortical tumors have most often been carcinomas, but on the whole they are rare.

When adrenocortical tumors alter the sex characteristics, the change is due to hyperproduction of androgens or estrogens respectively. Chorionepithelioma of the testis is the testicular tumor which most often gives rise to gynecomastia. In a few cases of other malignant testicular tumors, such as seminoma and embryonal carcinoma, the genesis of the gynecomastia perhaps may be due to the prevention of the testicular function by the tumor rather than to any endocrine function of the tumor itself.

The feminizing testicular tumor reported by the author in this paper was observed in a man 28 years old, in whom gynecomastia had developed in a couple of years. In addition, there was atrophy of the non-tumor-bearing testis, increased excretion of estrogen in the urine, but no output of gonadotropin and no disturbance of sexual potency. After removal of the tumor, the estrogen output decreased to normal, the gynecomastia subsided almost completely within 2 years, and the other testis increased to normal size. The tumor removed was a little larger than a hazel-nut, well-defined, localized to the hilus of the testis, and on section the cut surface was yellowish-orange in color.

Histologically, the tumor showed no resemblance to any of the tumors usually occurring in the testis. According to its structure, and the arrangement and character of the cells, it resembled a tumor arising from chromaffin tissue. There was no histological evidence of malignancy, although there was an unusually large number of cells and many mitoses.

As to the nature of the tumor, the author discusses the more obvious possibilites of interstitial-cell tumor, paraganglioma and adrenal cortical tumor. On

STUDIES IN CORPUS LUTEUM FUNCTION

J. S. L. BROWNE, J. S. HENRY, AND E. H. VENNING

McGill University and Royal Victoria Hospital, Montreal, Canada

J. Clin. Endocrinol., 7: 446, 1947

Sodium pregnanediol glucuronidate was determined by the method of Venning and correlated with endometrial biopsies. In 21 cycles in 20 cases biopsies showed no progestational changes when taken just before the onset of menstruation, and the pregnanediol in the same cycle was absent. On no occasion was the pregnanediol positive in a cycle in which the biopsy showed no progestational change. In 45 cycles in 36 cases the biopsies showed early or late progestational changes, and this was well correlated with the time of onset of the presence of pregnanediol. On 10 cycles in 8 cases the biopsies showed progestational changes but no pregnanediol was present in the same cycle; some of these discrepancies are explicable on the grounds of very large volumes of urine which prevented the detection of pregnanediol.

The effect of chorionic gonadotropin on pregnanediol excretion was further studied. If chorionic gonadotropin is administered in a dose of 1000 international units daily early in the luteal phase, in some instances a marked increase in estrogen excretion occurs. The excretion of pregnanediol is prolonged and endometrial biopsies show histological changes similar to those seen in early pregnancy.

THE METABOLIC PATHWAY OF ESTRIOL PRODUCTION IN THE ORGANISM

M. N. HUFFMAN AND A. GROLLMAN

Southwestern Medical College, Dallas, Texas

J. Clin. Endocrinol., 7: 453–454, 1947

The existence of a reversible equilibrium between estrone and a-estradiol and the conversion of the former to the latter in the human is well established, but the pathway of the conversion of estrone to estriol is still a matter of speculation. It is generally assumed that estrone is enolized and then hydrated to give estriol or that this hypothetical enol compound is formed directly by dehydrogenation of a-estradiol.

The writer suggests an alternative hypothesis; viz., that estrone is first converted to 6-keto-estrone which in turn is reduced first to 16-keto-a-estradiol and finally to estriol. Huffman has prepared an epimer of estriol in which both C_{16} and C_{17} have a-configurations. This compound has been designated as iso-

clearly delineated the enlargement of both adrenals, and exploratory laparotomy with biopsy of the right ovary confirmed the essential feminine constitution of the patient.

The hyperplastic left adrenal gland was completely excised and at least one third of the hyperplastic right adrenal was resected. The vagina and urethra opened into a narrow urogenital sinus requiring a plastic perineal operation. The greatly hypertrophied clitoris was amputated.

The excretion of urinary androgens (17-ketosteroids) was elevated prior to operation. Following adrenalectomy, there was a decided decline in urinary androgen excretion, which, however, still remained considerably elevated.

Striking clinical improvement occurred after the adrenal resections with the onset of cyclic vaginal bleeding, growth of the breasts, and a remarkable mental transformation. The body assumed a femine conformation, but the excessive growth of hair was not affected. The total amount of adrenal tissue surgically removed in this patient represents, the author believes, the largest amount excised in man without fatal outcome, and the absence of deficiency symptoms indicates that the upper limit was not exceeded.

Female pseudohermaphroditism, although uncommon, is not extremely rare. The author has now under observation three such patients, and Young reported 4, 3 of whom were subjected to partial resection of the adrenal glands. In 1, a 5 year old girl, the result was good. In the remaining 2 patients, however, sisters aged 15 and 13½, there was no breast development or vaginal bleeding following bilateral partial adrenal resection. Broster excised an entire adrenal in an adult without striking improvement, and concluded from this that these patients should be operated before the onset of puberty. It seems likely that an insufficient amount of hyperplastic adrenal tissue has been resected by these investigators and that the situation may be analogous to the surgical treatment of hyperthyroid before subtotal thyroidectomy was employed.

The amount of adrenal tissue necessary for the maintenance of life and health has not been determined, nor has it been possible to maintain life with adrenal cortical extract and desoxicorticosterone following total excision of both adrenals.

In the case reported above, the entire left adrenal gland was enucleated and at least one-third of the right adrenal resected. Furthermore, it is evident that in mobilizing and excising part of an adrenal gland, necrosis due to trauma, infarction, and infection, may compromise considerable more tissue than is actually cut away. On the other hand, it is likely that less hyperplastic than normal adrenal tissue is required for life maintenance.

(While the association of certain cases of female pseudohermaphroditism with adrenal lesions has long been known, the first thought is apt to be of a cortical tumor rather than a cortical hyperplasia. It is well to remember that the latter is the more common finding, as the author states.

A good many years ago I encountered a case almost identical with the one described by Wilhelm, though the outcome was not so happy, as the patient succumbed shortly after the operation. The autopsy, performed by the late Dr. W. S. McCallum, showed a remarkable bilateral hyperplasia of the adrenal cortex. It is in this type of case, more than any other

the basis of the histological features and the endocrine function of the tumor, the author arrives at the conclusion that presumably it was an aberrant adrenal cortical tumor, developed from accessory adrenal cortical tissue located in the hilus of the testis. 2 figures.

(While the article abstracted above deals with tumors in the male, it is of interest in that it contrasts the sex character influence of certain tumors in the male with the well known masculinizing or feminizing effects of certain neoplasms of the female gonad. Since the tumors which produce feminization in the male are, as stated by the author, of adrenal origin, a better comparison would be with the adrenal rather than the ovarian tumors encountered in the female. The effects of these are in the main of heterosexual nature. If they arise in fetal or early postnatal life, such tumors even bring about pseudohermaphroditism. At a somewhat later stage they may cause a heterosexual type of precocious puberty, usually not associated with precocious menstruation. When they arise in still later life, much lesser degrees of intersexuality are noted, usually some form of virilism, characterized by hirsutism, flat breasts, deep voice, masculine gait and perhaps some degree of hypertrophy of the clitoris.

It is of interest that the effects of the tumor reported by Ostergaard were likewise heterosexual, i.e. feminizing. As to the mechanism involved with either the male or the female adrenal tumors, we are still completely in the dark. Certainly the hormone involved is not cortin, and there must be other as yet unknown adrenal principles which play an important role in the phenomena of sex differentiation. The close embryological intimacy of the adrenal cortex and the ovarian medulla makes it easy to understand why certain tumors of the former and the arrhenoblastomas arising in the latter produce such similar effects in the female.

The testicular tumor which is characterized by gynecomastia is the teratoma, this effect being explained by the gonadotrophic production which has its source in the chorionepitheliomatous elements so often found in teratoma. Even so, it is difficult to explain the hormonal reactions which lead to the appearance of the gynecomastia which is the chief biological symptom in such patients. As to the seminomas, which are histogenetically and histologically identical with the dysgerminoma of the female, it is difficult to accept the author's suggestion that an associated gynecomastia may be due to "prevention of the testicular function by the tumor." This would predicate a hormone function in this group of tumors, and the evidence against this is quite complete. It seems more likely that such an effect is due to small and often undemonstrable chorionepitheliomatous areas in the teratomatous growths which in a considerable number of cases have been found in association with dysgerminoma.—Ed.)

RESECTION OF HYPERPLASTIC ADRENAL GLANDS FOR FEMALE PSEUDOHERMAPHRODITISM

SEYMOUR F. WILHELM

The Urological Surgical Service of the Beth Israel Hospital, New York, N. Y.

A case of female pseudohermaphroditism, due to bilateral hyperplasia of the adrenal glands is reported. Laminography following perirenal insufflation

TRUE HERMAPHRODITISM: REPORT OF A CASE WITH AN OVOTESTIS, AND ENDOCRINE STUDIES

J. C. WEED, A. SEGALOFF, W. WIENER, AND J. W. DOUGLAS

Charity Hospital of Louisiana and the Alton Ochsner Medical Foundation, New Orleans, Louisiana

A colored "female", aged 36 years, exhibiting feminine bodily contours and feminine social adjustments, was found to have an enlarged clitoris, masculine facial hair distribution and abnormal external genitalia. In a large hernial sac, an ovotestis was found associated with an atrophic uterus, left tube and ovary. Biopsy sections of the latter revealed normal ovarian stroma and a small Brenner tumor. Sections of the ovotestis, which was completely removed, showed normal ovarian stroma, definite testicular tubules without spermatogenesis, and large islands of interstitial cells. Also found in the hernial sac were a rudimentary epididymis and fallopian tube. The urinary gonadotropic hormones remained essentially unchanged in preoperative and postoperative assays. The 17-ketosteroid determinations were 7.5 and 7.6 mg. per 24 hours preoperatively and from 4.8 to 5.6 mg. per 24 hours postoperatively.

(The secondary sex character abnormalities seen in the various forms of intersexuality are not in any way distinctive. Those described by the authors for this case of what is apparently true hermaphroditism could just as well have been seen with either the male or female types of pseudohermaphroditism. The authors' comments on the urinary hormone findings are in conformity with those of others who have made such studies in intersexual conditions, with what seems like general agreement as to the very limited value of such studies.—Ed.)

variety of intersexuality that one is most likely to find that the urethra empties into the anterior wall of the vagina a few centimeters above the introitus. This abnormality was found by Wilhelm in this case, and it was present also in mine.—Ed.)

SOCIAL AND PSYCHOLOGICAL READJUSTMENT OF A PSEUDOHERMAPHRODITE UNDER ENDOCRINE THERAPY

RITA S. FINKLER

Newark, New Jersey

J. Clin. Endocrinol., 7: 456–457, 1947

An intersex individual, aged 21, raised as a female, failed to develop either male or female secondary sex characteristics at puberty. The patient was asthenic and lacked endurance and energy, but excelled scholastically; the psychological status was of masculine pattern. At the age of 19 he developed an emotional attachment for a girl and at the same time became aware of an enlarged clitoris. This discovery resulted in symptoms of anxiety neurosis which lasted for over 2 years until a thorough investigation revealed the individual to be an "unfinished male." The investigation consisted of bio-assays, psychological analyses and exploratory laparotomy. Intensive substitution therapy with various testosterone compounds developed male secondary sex characteristics, and caused marked improvement in the patient's general health, energy, endurance and outlook, on life. The patient was stimulated to still further scholastic achievement. As long as therapy was continued, the physical and psychological status continued to improve; interruption of therapy for any appreciable length of time resulted in diminution of energy, endurance and mental alertness.

(This paper has not at this writing appeared in its complete form, the above being an abstract prepared by the author before the last meeting of the American Association for the Study of Internal Secretions. It is perhaps unfair to comment on it now, but I gather that this individual of 21 was raised as a female and then, after study, consigned to the male way of life. I hope that there was some good reason for inflicting such a tragic upheaval on this patient, as none appears in the data included in the author's abstract. It seems to me that it would take more than endocrine treatment to prevent the emotional and psychological upheaval to be expected after such usually ill-advised attempts at reconversion in adult life. When the paper is published in complete form it will be commented upon again, and some explanation may appear for the line of treatment selected for this patient.—Ed.)

dence of functional activity was associated with an endometrium like that seen in an anovulatory cycle. Such observations, should they prove to be at all common, would obviously be of importance in the interpretation of endometrial biopsy. We shall comment more fully on Brewer's paper in the next issue of the Survey.—Ed.)

ORAL ESTROGEN THERAPY DURING MENOPAUSE

ABBEY D. SELEY, DEBORAH BAUMGOLD, AND S. VERNICK

Hospital for Joint Diseases, New York City

J. Clin. Endocrinol., 7: 451, 1947

Management of the menopausal state by oral estrogens alone was begun on July 1, 1943, in this hospital and for the past 3½ years not a single injection of any estrogen substance has been given. A comparative clinical study of 90 unselected consecutive patients was initiated in order to evaluate the effectiveness of oral estrogens. It is the purpose of this report to indicate the relative value of the various estrogenic substances used in regard to: (1) ability to control the neurocirculatory disturbance; (2) the rate of change of the vaginal smear; (3) the possibility of carcinogenic alteration when estrogens are used in doses sufficient to control the menopause, as evidenced by endometrial biopsy and biopsy or curettage of the cervical stump; (4) the number and type of side reactions including bleeding; and (5) the final result obtained by the oral route alone a) in the average case and b) in cases complicated by menopausal arthralgia.

(No results are reported by the author in this paper, but I would like to compliment him on the fact that "for the past 3½ years not a single injection of any estrogen substance has been given" in the treatment of menopausal symptoms. Hypodermic estrogen medication is both unnecessary and undesirable for this indication, as I have repeatedly urged in comments on the general subject.—Ed.)

THE MENOPAUSE

F. D. COLEMAN

Louisville

Kentucky M. J., 45: 207–209, 1947

The author states that the menopause is one of the most therapeutically abused conditions encountered in medical practice. We are far too eager, usually, to come forth with a needle and an estrogenic.

The climacteric is discussed in respect to the varied clinical picture which it may present. The anatomical and physiological changes involved are described.

THE MENSTRUAL CYCLE

CORRELATION OF BASAL BODY TEMPERATURE CURVES WITH ENDOMETRIAL BIOPSY

A. R. ABARBANEL

College of Medical Evangelists, Los Angeles, California

Correlation studies of several hundred endometrial biopsies with the basal body temperature curve reveal that on the whole the classically sharply defined diphasic B.B.T. curve is usually associated with a presumed ovulatory cycle as witnessed by successful conception or a fully developed secretory endometrium. On the other hand, study of various aberrations revealed a secretory endometrium, especially of the so-called mixed type or immature progestational phase (day 19–22 of a 28-day cycle) when taken the first day of the menstrual period. B.B.T. curves were either irregular or flat.

The author postulates that an immature progestational phase of a mixed type of endometrium does not necessarily represent ovulation, but merely various degrees of theca luteinization without concomitant ovulation.

(Anyone who studies large numbers of endometria knows that there is wide individual variation in the endometrial response to both estrogen and progesterone. An endometrium removed, for example, on the 27th day of the cycle may show such a pronounced progestational response that it cannot be distinguished from an early decidual phase. The endometrium of another woman removed on exactly the same day of the cycle may show a far lesser degree of response. Again, in one case the progesterone effect is apparently exerted on the glands and epithelium, with little or no predecidual change in the stromal cells. In another the latter appear especially sensitive to progesterone, so that they look like the genuine decidual cells of pregnancy. And yet in all such cases the custom has been to consider a definite progestational response as evidence that ovulation has occurred. It is true that theoretical objections have been urged against this view, with the suggestion that, even without the extrusion of an egg, the follicle may go on to form a corpus luteum, or that at times theca cells surrounding atretic follicles might give off enough progesterone to evoke a progestational effect in the endometrium. Thus far, however, there has been no worthwhile evidence to substantiate these suspicions, and I doubt that the report of such discrepancies, as based merely on basal temperature records and not supported by correlated study of the ovaries, will be sufficient to shake our faith in the general reliability of a definite progestational response as an index of ovulation. It is true that Abarbanel applies his comment only to cases showing a very immature secretory response, corresponding to the average 19th to 22nd day picture, but in these early cases there is much more room for error in the interpretation of secretory activity, unless differential staining is resorted to.

On the other side of the picture the question may be raised as to whether the absence of a progestational picture may be considered a safe index of the nonoccurrence of ovulation, and on this point it seems possible that mistakes might occur. Here again the evidence has been pretty slim, but a paper by Brewer, which has appeared just as these lines are written, includes at least one case in which a definite corpus luteum with histological evi-

least 85 per cent of normal women have no trouble, and the mere fact that a woman is passing through the menopause is no indication for endocrine therapy. Any disturbance of the climacteric which is primarily due to the relative deficiency of estrogenic secretion can always be alleviated by suitable administration of estrogenic hormones. The duration of therapy depends upon the individual response to therapy and should always be directed toward an early withdrawal of the glandular therapy. Contraindications to estrogen therapy and some of the untoward effects of estrogen therapy are outlined. Androgen therapy is not at effective as that with estrogens, but can be used for relief of certain discomforts when other methods have failed. One should always rule out carcinoma before administering androgens.

(See comment below on paper by Foltz.—Ed.)

PSYCHIATRIC ASPECTS OF MENOPAUSE

L. M. Foltz

Louisville

It is felt that the personality plays a larger role in the whole symptom picture of menopause than the cessation of glandular activity itself. Studies of the premenopausal personalities of those suffering severe disturbances at the menopause indicate sensitive, rigid, stay at home, "mind their own business" attitudes. A woman who has lived unwisely between the ages of 12 and 45 can build up a great many regrets over which to become depressed when the menopause appears. In addition, a woman at this time of life faces many factual circumstances that are difficult for her to surmount.

In the writer's opinion, the changing physiology of the ovarian activity could take place without any distress in most women. Probably the slowing down and cessation of ovarian activity places an added burden on the already maladjusted and emotionally immature personality.

Most endocrinologists now believe that a patient suffering from the menopausal syndrome at the climacteric should have an ample course of estrogenic therapy, and if this brings no improvement it indicates that the psychiatric aspects of the case should be investigated. The author believes that an effort should be made to investigate personality factors before such treatment begins, so that the patient could benefit from both measures. If cases are given the benefit of early psychotherapy, the prognosis is much better. It is unwise to continue estrogenic therapy when a patient does not improve in a relatively short time or has recurrences of symptoms.

Fifteen to 20 per cent of women will pass the menopause without the occurrence of noticeable unpleasant symptoms; 10 to 12 per cent will have incapacitating symptoms; and the remainder will have symptoms of varying degrees of intensity. Menopausal patients should be put into 2 categories: those actually suffering from severe symptoms, and those who are suffering from symptoms which they have been told or have read they are supposed to be suffering from. Frequently, the menopause acts as a trigger mechanism by which previously present and latent symptoms are exaggerated or allowed full expression.

Treatment of the menopausal patient should never be started until a carefully correlated history has been taken, and a thorough physical examination done. A search should be made for malignant disease or other organic disease which might account for, or in some way, color the symptomatology. The presence of neoplasm, especially in the generative tract or breasts, is a definite contraindication to the use of estrogens. A fairly large percentage of menopausal patients need only an explanation of what is happening to them and reassurance in regard to their fears and apprehensions. They should get ample sleep, mild sedation, if necessary, a reasonable amount of exercise, and a well balanced, regular diet suited to the weight situation of the patient. If symptoms are not relieved by mild sedation (phenobarbital is probably the drug of choice), hormonal therapy should then be started. The preferred route of administration is oral, and the preferred medication is usually one of the synthetics. At all times, we should keep in mind the important dangers of estrogen therapy: (1) artificial prolongation of menopausal symptoms; (2) production of benign glandular-cystic endometrial hyperplasia; and (3) pre-malignant and malignant endometrial changes.

The writer completes his discussion of the climacteric by describing the male counterpart of the so-called menopause, and discussing its treatment.

(See comment below, on paper by Foltz.—Ed.)

MENOPAUSE FROM THE VIEWPOINT OF THE GYNECOLOGIST

W. O. JOHNSON

Louisville

Kentucky M. J., 45: 209–212, 1947

The author discusses the variations and gradations in hormonal and histological phenomena which occur at the menopause, as well as the psychological disturbances to which climacteric women are susceptible. The menopause cannot be diagnosed from subjective symptoms and age, but must be made on careful analysis of physical, physiological and psychological conditions of the patient, and treatment should be carried out as indicated in the individual case. A woman of sound mind and body takes the "change of life" in her stride and at

THE UTERUS

HYPERTROPHY OF THE ENDOMETRIUM

HERBERT F. TRAUT (San Francisco, Calif.), ADDISON B. SCOVILLE (Nashville, Tenn.), AND ALBERTA KUDER (New York, N. Y.)

The Department of Obstetrics and Gynecology of Cornell Medical School and of the University of California Medical School

Localized hypertrophic changes in the mucosal lining of the uterus, such as endometrial polypi, are easily recognized and quite well understood; on the other hand, diffuse hypertrophy, aside from the physiological hypertrophy of the normal menstrual or pregnant cycle, is apparently not widely known and is, it seems, frequently confused with hyperplastic or adenomatous conditions of this membrane. There is no complete and careful consideration of diffuse hypertrophy of the endometrium as such in the literature of recent time, and certainly none of any date with illustrations which would enable the student to differentiate this condition from hyperplasia of the endometrium, with which it is not infrequently confused. It seems justifiable, therefore, to attempt to elucidate this interesting adenopathy of the uterine mucosa.

Four hundred and forty-five uteri have been studied after fixation, as outlined above. The endometrium has been stained usually with hematoxylin and eosin, but whenever the question of secretory activity was to be decided, Best's carmine stain for glycogen has also been made.

Four hundred and four of the uteri were myomatous, while only 41 contained no tumors. Of these, 201 were accompanied by the ovaries which were studied in correlation with the endometrium. In the total material, it was found that 30 had cystic glandular hyperplasia of the endometrium (6.6 per cent), while 176 had a definite hypertrophy (39.6 per cent). The non-myomatous uteri alone had a somewhat higher incidence of hypertrophy (25.7 per cent), and a lower one for cystic glandular hyperplasia (5.8 per cent). Hypertrophy of the endometrium therefore is not found only in myomatous uteri, as many have thought, for the non-myomatous uteri in this study showed an incidence of nearly 26 per cent.

Whereas cystic glandular hyperplasia was constantly associated with the follicular phase or follicular cysts of the ovary, the hypertrophy was found in both the proliferative and secretory forms and accompanied by the follicular or lutein phase of the ovary respectively.

If the morphological differences in the endometrial picture were the only criteria for differentiation between cystic glandular hyperplasia and hypertrophy, the demonstration would be more difficult and less convincing, particularly in

(The first two of these three papers, those by Coleman and Johnson, are written from the gynecological point of view, and both embody good advice on such things as avoidance of estrogenic therapy unless clearly indicated by the severity of vasomotor symptoms, the undesirability and possible hazard of excessive or too prolonged estrogenic therapy, and other such matters. Certainly the majority of menopausal women need no estrogen therapy at all, but in the comparatively small proportion of women who do, it is of definite value in tiding them over the symptomatic rough spots, when used conservatively, intermittently and not too long.

The third paper, by Foltz, I would judge is written by a psychiatrist, as the approach to the problem is characteristically different, with the chief accent on personality factors and psychotherapy. While we are accustomed to poke fun at the complicated terminology of psychiatrists, and the nebulousness to most of us of many of their discussions, no sensible gynecologist would deny the importance of educational and psychiatric measures in many cases. In the simpler ones, which are greatly in the majority, he ought to be able to qualify as an amateur psychiatrist himself; in the occasional severe case, he will seek the cooperation of the trained psychiatrist.—Ed.)

however, the secretory activity is early or questionable, the answer may be sought through the aid of the glycogen stain.

In the proliferative phase, however, the differences are not so striking and one may well make errors until the eye is trained to note the regularly spaced epithelium of the glands and the paucity of epithelial cells as compared with hyperplasia, in which condition they are usually markedly increased in number. Cystic glands may occur in both conditions, although they are much more characteristic of hyperplasia than of hypertrophy.

There is no agreement as to the cause. It seems reasonably clear, however, that in contra-distinction to true cystic glandular hyperplasia, the cause is not hormonal in nature. At least it is impossible to ascribe it to the ovarian hormones or the lack of any of them as we understand them today. One should bear in mind, however, the possible relationship of other hormonal factors, perhaps those of the anterior hypophysis. Certainly the fact that the condition seems to be progressive during the reproductive period and then diminishes very markedly thereafter, strongly suggests a relationship with the reproductive forces of the body. However, it appears more likely that it is a form of trophic disturbance resulting from prolonged passive congestion and excessive edema, and that in all likelihood those factors such as tumors, torsions of the uterus, and malpositions which may be associated with stasis of the lymph and blood stream are the responsible ones.

From the clinical point of view, hypertrophy of the endometrium has little or no significance in itself. It is important, however, to differentiate it from cystic glandular hyperplasia which, having great clinical importance, is often confused with it. Hypertrophy is not a common cause of abnormal endometrial bleeding when it is of the diffuse type. Localized hypertrophy or polypi, on the other hand, are frequently hemorrhagic because of necrosis of the tips of the elongated structures which have outgrown their blood supply.

(There is no doubt of the occurrence of what appears to be a genuine hypertrophy of the endometrium, an overgrowth not only macroscopically, but also expressed histologically by the larger size of the epithelial cells and the glands. Simple hyperemia and consequent overnutrition would not seem to explain the condition adequately, for certainly it is often lacking in many cases in which the blood supply is enormously increased, as in the case of large myomas. A similar hypertrophy may also involve the myometrium, the uterus being of much larger than normal size, in the absence of any pathological lesion. Perhaps such hypertrophy may be considered analogous to the abnormal pubertal hypertrophy of the breasts which one sees from time to time. In none of these is there any characteristic increase in the estrogens, and it has always seemed to me that the only possible explanation is that the genital or mammary tissues of some women, for some unknown congenital or chromosomal reason, are abnormally sensitive to the growth effect of the estrogenic hormone.—Ed.)

the borderline cases. However, the fact that hypertrophy responds to the ovarian hormones in a manner closely simulating that of the normal menstrual cycle, at once proves quite conclusively the vast difference that must lie behind their respective origins. The secretory phase of the hypertrophic membrane is most characteristic, the proliferative phase less so, although the cells of the glandular epithelium are consistently larger, while occasionally in borderline instances it is extremely difficult to decide between hyperplasia, hypertrophy and normal endometrium in this phase. However, after carefully studying the growth characteristics of the hypertrophic form, it becomes possible to differentiate them with a fair degree of accuracy.

HISTOLOGY OF HYPERTROPHY OF THE ENDOMETRIUM

The thickness of the endometrium is markedly increased, being often 5 mm., and sometimes even 1 or 1.5 cm., from the uterine cavity to the muscularis. The surface is apt to be wavy and sometimes approaches blunt polyp formation. It may occur in uteri which are normal in size, as well as in those in which myomata are present. In the myomatous uteri it is more apt to be found in the recesses of the cavity removed from the tumor, particularly if they be submucous.

Microscopically the glands are increased in size and occasionally they are cystic, which undoubtedly has led to the confusion with cystic glandular hyperplasia. In the proliferative phase, they may be widely separated by an edematous stroma, whereas in the secretory phase, the glands are often so numerous as to leave little intervening stroma. In addition, the longitudinal contour of the glands tends to a lesser degree of tortuosity than in the normal proliferative or secretory phase.

The finger-like papillary structures so characteristic of the normal secretory endometrium are not seen, or are much blunted and are markedly reduced in number.

The glands tend to be lined by a single row of columnar cells which are much larger than normal and are sharply defined against the lumen in both the proliferative and secretory phases. These cells always appear to contain an excess of cytoplasm which is much less basophilic than normal. The nucleus is oval or round and is seldom found occupying the base of the cell, as a globule of cytoplasm tends to collect in that location. There is seldom any tendency toward multiplication of layers or "heaping up" as is so commonly seen in hyperplasia, although in the proliferative phase one sometimes sees this to a moderate degree.

The stroma cells are usually round, even in the proliferative phase, especially if edema be present, which is particularly apt to be the case at the periphery. In the deeper portions the stroma may be more compact and the cells spindle shaped. The staining reactions are quite uniformly basophilic and pale.

The vessels commonly show thin walls and over-distention, as though passive congestion were quite constant.

Differentiation between hyperplasia of the endometrium and hypertrophy in the secretory phase offers no possible obstacle in characteristic specimens. If,

EPITHELIOMA OF THE UTERINE CERVIX

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In spite of more efficient methods of treating cancer and extensive educational
programs to help the medical profession and the laity to recognize the early
signs of this disease, we are confronted with the appalling fact that one death out
of every 17 is from cancer.   Statistics also show that more women die as the
result of cancer of the uterus today than previously.   In 1936, 16,280 women
died in the United States from uterine cancer and of this number the uterine cer-
vix was the seat of the primary lesion in about 11,000 cases.

If the presence of cancer is once accurately diagnosed by examination of a
microscopic section, permanent cure can be obtained only by radical and effi-
cient treatment.   The type of treatment and the ultimate result of such treat-
ment will depend, not only on the extent of the disease, but also in large measure
on the grade of malignancy present, as suggested by Broders and Martzloff.
(Obstetrics and Gynecology.   Philadelphia, W. B. Saunders Company, 2: pp.
59, 833, 1933.)   Broders' classification, which takes into consideration the
amount of differentiation of the cells in the active, growing portion of the tumor,
is of great prognostic value.   In a tumor of grade 1, there is little departure
from the normal type of adult cell and, as a result, such tumors are of low degree
of malignancy.   Tumors of grades 2 and 3 show less differentiation and those
of grade 4 show marked differentiation and represent the most active type of
malignant disease.   Many pathologists do not place much value on the grading
of malignant tissue and contend that sections from different parts of a single
growth will suggest different degrees of malignancy.   It has been said that
tissue taken at different times may show various percentages of differentiation
of the cells.   There is no doubt that changes do take place and various factors
like infection, degeneration and so forth, influence the microscopic picture.   After
trial in a very large series of cases, however, the authors are satisfied that the
method is of real prognostic value and they rely on it a great deal.   (See Table
I.)   There is no doubt that the training and personal equation of the pathologist
are most important in evaluating the method.

It is hard to compare statistics of the present day with those tabulated from
results obtained before the use of chemotherapy, scientifically given anesthetics
and improved surgical technic with more importance placed on preoperative
and postoperative care including transfusions, intravenously administered fluids
and the diagnosis and treatment of atelectasis, pneumonia, peritonitis and venous
thrombosis.   Furthermore, in the earlier statistics in the Mayo Clinic many
operations performed for cancer of the cervix were listed as simply "total abdom-
inal hysterectomy" and it was difficult to tell from the specimens whether a

FIBROMYOSIS UTERI: ENDOMETRIAL TYPE

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This report is one of a uterine growth which resembles adenomyoma but is not a true endometriosis, because microscopically it does not contain glands. It is termed "fibromyosis uteri, endometrial type."

The patient was a 46 year old white lady who was hospitalized because of profuse menstrual bleeding and a lump in her lower abdomen of 7 months duration. A subtotal hysterectomy was performed without event. The specimen measured 12 cm. in diameter and was an asymmetrically enlarged uterus due to intramural masses of stromal cells and hyperplastic smooth muscle.

Microscopically broad masses of cells could be seen infiltrating between the bundles of smooth muscle. Apparently these were derived from the endometrial stroma. No endometrial glands were identified in the specimen.

It is the author's opinion that the stromal cells arise from mesenchymal cell rests laid down during development of the müllerian ducts and that with endocrine stimulus hyperplasia of these endometrial stromal cells and the myometrium takes place.

These tumors seem to have a limited capacity for growth and patients in whom all the growth is contained in the uterus are probably cured by operation. However, if there is extension into the parametrium the likelihood of recurrence is good.

(It would appear from the author's description that the lesion encountered in his patient was one to which attention was directed by Robertson, Hunter, Larson and Snyder in 1942 (Amer. J. Clin. Path.,**12**: 1, 1942), and for which some such designation as stromal adenomyosis seems appropriate. It differs from ordinary adenomyosis in that the endometrial elements which benignly invade the myometrium are entirely stromal with no glandular elements at all, though why there should in such cases be a selectiveness of this sort is not clear. A similar stromal dominance is seen in rare cases of endometrial hyperplasia, as was described by Novak and Martzloff in 1924. (Am. J. Obst. & Gynec., **8**: 385, 1924.) In stromal adenomyosis, the invading stroma cells can be shown to be directly continuous with the surface endometrium from which they arise, so that it is unnecessary to invoke any such hypothetical explanation as that suggested by Hill. The malignant prototype of this lesion, sometimes spoken of as malignant stromatosis, is actually only one form of endometrial sarcoma.—Ed.)

decided change in the treatment of carcinoma of the cervix followed the discovery of radium and improvement in x-ray equipment. In most gynecologic clinics radium and deep roentgen therapy largely supplanted surgical treatment. This change was largely to be attributed to the poor results obtained when surgical treatment was the only recognized type of treatment for all cases. One reason for the poor results of surgical treatment even in cases of operable carcinoma was that an incomplete operation was frequently done, with rapid recurrence of the malignant lesion. In other cases a radical procedure was attempted by a surgeon who was not experienced in this special type of operation and the tedious dissection of lymph nodes that is necessary, and high mortality and morbidity rates resulted. In still other cases surgical treatment was attempted in cases of hopelessly inoperable carcinoma and an incomplete operation resulted.

In recent years, following the introduction of chemotherapy and the realization of the importance of the modern methods of postoperative care, more and more surgeons are treating these patients surgically, especially by the Wertheim type of operation. If only good surgical risks in group 1 or 2 are accepted the mortality rate should not be much more than that following hysterectomy for benign conditions.

There is no doubt that efficient surgical treatment, when attempted only in suitable cases and by surgeons accustomed to the tedious dissection necessary and when combined with modern methods to protect the patients from infection and other postoperative complications, gives a relatively high percentage of cures with a very low mortality rate. When such treatment is given in conjunction with irradiation under the direction of an expert in this field of therapy, the results are so good that the authors feel that further trial is justified in spite of the encouraging results obtained by irradiation alone.

(The series of cases reported by the authors from the Mayo Clinic is large, and justifies them in expressing certain convictions. They appear to place considerable value upon the histologic cell gradation of cervical carcinoma, contrary to the relative unimportance of this factor in the minds of many gynecologists and radiologists. The comparative results obtained in the various grades seem to support their view. As a matter of fact, they state that "the extent of the local growth does not represent as good a guide to the ultimate outcome as the histologic appearance of the predominant cells," again a viewpoint which will not be endorsed by all. While they feel that a selected group of early cases justify operations of the Wertheim type, they emphasize that these constitute only a very small proportion of the entire number. The five year results reported for the entire series of 2179 cases, as given in Table 3, compare very favorably with those of other clinics. Finally, in view of the intensive cancer campaign of the past few years, it is discouraging to read that cases are not being seen at the clinic at earlier stages than was the case 25 years ago.—Ed.)

more radical operation was done than is indicated in benign conditions. Table I shows the 5-year results obtained according to grade of malignancy in 392 cases of epithelioma of the cervix in which operation was performed at the Mayo Clinic from 1913 through 1940. In 81 cases the operation performed was listed as Wertheim hysterectomy whereas in 311 cases it was |listed simply as total hysterectomy (abdominal or vaginal).

TABLE I

Effect of grade of malignancy (Broders' Method) on prognosis following operation for epithelioma of cervix (1913–1940)

GRADE	WERTHEIM HYSTERECTOMY			ALL PATIENTS OPERATED ON		
	Patients traced*	Lived 5 or more years after operation		Patients traced*	Lived 5 or more years after operation	
		Number	*Per cent*		*Number*	*Per cent*
1	0	0		3	3	. 100.0
2	13	12	92.3	50	32	64.0
3	44	29	65.9	179	106	59.2
4	20	10	50.0	99	37	37.4
Not Stated	4	2	50.0	61	29	47.5
Total.....	81	53	65.4	392	207	52.8

* Inquiry as of January 1, 1946, includes only those patients operated on 5 or more years prior to the time of inquiry; that is, 1940 or earlier. Hospital deaths are included in the calculations.

TABLE III

Epithelioma of the cervix
Five Year Survival Rates by Type of Treatment

TYPE OF TREATMENT	PATIENTS*		LIVED 5 OR MORE YEARS AFTER TREATMENT	
	Total	Traced	Patients	Per cent of traced patients
Operation without irradiation........	259	247	75	30.4
Operation with irradiation..........	350	297	161	54.2
Irradiation only....................	1,570	1,328	470	35.4
Total........................	2,179	1,872	706	37.7

* Inquiry as of January 1, 1945. Included are only those patients operated on or treated 5 or more years prior to the time of inquiry; that is, 1939 or earlier. The hospital deaths are omitted from the calculations.

Table III shows the 5-year survival rates by type of treatment for a series of 1,872 traced patients from 1910 to 1939, inclusive. After a critical analysis of the results obtained in the past either by the Wertheim type of abdominal hysterectomy or by Schauta vaginal hysterectomy, taking into consideration the operative mortality rate and the expectation of life following operation as recorded by surgeons both in this country and abroad, it was not surprising that a

differentiates the less is its malignancy and the less is its radiosensitivity. Also the prognosis in adenocarcinoma of the cervix is not as favorable as in the squamous cell type. Since the differentiated spinal cell tumors and the adenocarcinomas do not respond well to irradiation, especially when found early (27 per cent 5-year survival rate) they may be better suited to surgery.

In the relation of age of the patient to prognosis the results of this study show no relationship whatsoever. The duration of symptoms was also found to be a poor index to the extent of the disease. However, in general, the longer the history the more extensive the carcinoma and the poorer the prognosis.

In two-thirds of the cases the initial symptom was hemorrhage and in 14 per cent the first symptom was pain in the back, groins or abdomen. Usually the presence of pain is indicative of advanced disease. Hence if the symptom of pain is present it makes for a poor prognosis.

The survey shows again the importance of early diagnosis. The single most important factor controlling permanence of cure is the extent of the carcinoma when treatment is instituted.

(The results reported do not seem to differ greatly from those reported in the American clinics, being a little better than in some of the latter, not quite as good as those reported by some others. It would appear that the most popular plan of therapy in the European clinics is the Stockholm plan so ably described by its originator, Dr. J. Heyman, the Director of the Radiumhemmet, in a very recent paper (J. A. M. A., 135: 412, Oct. 18, 1947.)— Ed.)

COMPLICATIONS FOLLOWING RADIOTHERAPY OF CARCINOMA OF THE CERVIX UTERI

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Complications of radiation therapy still occur and are very troublesome in spite of the marked advances in methods of administration and the safeguards now being employed. Thorough pre-irradiation study of the patient, including urologic and bowel examinations, will help prevent complications. Psychologic preparation is of equal importance. Frequent and thorough periodic follow-up examinations are important in order to recognize the complications that may arise and to treat them.

Rectal complications, in the author's experience, have been the most frequently encountered and troublesome reactions. Rarely does a patient go through the cycle of therapy without manifesting some degree of proctitis; the natural course is toward a spontaneous cure in most cases. The late rectal reactions are serious and usually appear 6 months or more after irradiation. In

CANCER OF THE CERVIX UTERI: THE RESULTS OF TREATMENT WITH RADIUM

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This review includes a 20-year period between 1922 and 1941 during which time 837 cases of cancer of the cervix were seen at the Cardiff Royal Infirmary. They were grouped into the 4 League of Nations stages. Six per cent were stage I, 24 per cent stage II, 59 per cent stage III, and 11 per cent stage IV. Ten cases refused treatment.

Between 1922 and 1930 the total amount of radium employed was 1800 to 2400 mgm. hrs. Since 1930 the modified Stockholm method has been used. This comprised 2 exposures of 30 hrs., using 50 mgm. intracervically and from 75 to 120 mgm. contracervically with a platinum filtration of 1.5 mm. No deep x-ray therapy was employed.

Nine per cent were lost sight of within 5 years of treatment and for statistical purposes are considered "dead from cancer." All those who died of any cause whatsoever are considered "dead from cancer." Since this report is concerned primarily with the results of treatment as represented by the 5-year Survival Rate this figure would have been better with closer follow-up. The absolute Survival Rate (based on all cases seen, treated or not) was 21.4 per cent or 177 cases alive after 5 years. Of the stage I the absolute Survival Rate was 71.6 per cent, stage II 33.3 per cent, stage III 13.7 per cent and stage IV 4.5 per cent. In assessing results a 10-year survival after irradiation is not synonymous with cure.

The patients seen during the 1930 to 1941 period and treated by the Two-Application Stockholm Method have been discussed in greater detail. The life expectancy during the 5 year period after treatment of these 585 cases is 25.6 per cent (based on 3-year figures with 15 per cent deducted). This is in contrast to the interstitial radium treated group from 1922 to 1930 which had a 5-year survival rate of only 11 per cent.

Microscopically the tumors in this series are classified into 3 groups, spinal cell, transitional and spindle cell type. There was no significant relation found between the age of the patient and the cell type. However, the incidence of spindle-cell and adenocarcinomas was slightly more common in the older women and adenocarcinoma also had a slightly higher incidence in the nulligravidae. Carcinoma of the cervix appeared as an ulcer in 55 per cent of the cases and as a hypertrophic growth in 29 per cent (the symptoms appear earlier in the latter group and the patients' prognosis is better). The cell type in the hypertrophic group was adenocarcinomatous in over half the cases. In analyzing the prognosis in relation to cell type the general feeling is borne out that the more a tumor

frequent, as the present paper emphasizes. Some of these are serious and may be fatal, as in the case of the many serious intestinal injuries which have been reported. More often they are distressing but not fatal, as in the proctitis so often seen.

Any one who has encountered cases of so-called "factitious proctitis," with the pain and serious bleeding which it entails, and with its intractability to treatment, needs no argument to give him a deep respect for the possible hazards of radiotherapy, even in the hands of well qualified radiotherapists. And yet the fact that a number of the latter have been able to treat large numbers of such cases without encountering such serious sequelae justifies the hope that their general incidence should be greatly decreased with general improvement in technique.

Thomas' short paper should serve a useful purpose, not only in calling attention to the incidence of postradiation complications, but also in the valuable suggestions as to the management of many of them.—Ed.)

THE EARLY DIAGNOSIS OF CANCER OF THE UTERUS

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J. Philippine M. A., **23**: 1–3, 1947

The author discusses the importance of the problem of cancer of the uterus, stressing that the responsibility for cure rests on both the patient and the physician. The curability of all stages of cancer of the uterus in clinics abroad is about 25 per cent. In the experience of the author's clinic, the cases are so far advanced that not even a 5 per cent 5-year salvage is expected. Although medical science has the means to cure early cancer, those afflicted with cancer seek medical aid invariably a little too late. What factors are responsible for this situation?

Cancer of the uterus presents characteristics which we ought to be able to recognize. It appears more commonly in women close to, or at, the menopause. Its first manifestation is leucorrhea. This is followed by a disturbance in menstrual history taking the form of increase in the menstrual flow, prolongation of the period, intermenstrual bleeding, or post-menopausal bleeding. When pain is experienced, the disease is so far advanced that cure is difficult or impossible. According to the author's observation, the patient, either through ignorance or fear or superstition, allows an average of 6 months to elapse after the onset of symptoms before consulting a physician, and even then does so with reluctance. However, the blame for the high mortality from cancer of the uterus cannot be laid entirely on the patient. It is our duty as medical practitioners to offer a sustained educational program that would lead women to seek medical advice whenever abnormal vaginal bleeding occurs. Better still, women should be made to see the necessity of periodic complete physical and pelvic examinations as the only means to discover cancer at its earliest stage.

Even if this information were widely disseminated, however, it would be of

the writer's experience the incidence is about 5 per cent. Local overdosage of radium in the vaginal vault must be the main factor; however, some patients seem to have an unusual susceptibility. Every effort is made to protect the rectum by application of the radium under general anesthesia so that the vagina may be ballooned with a tight vaginal gauze packing. The process is a fibrosis and ulceration which may be limited to the rectal wall or more frequently involves the peri-rectal tissues. Sometimes a chordotomy or lumbar sympathectomy is required to relieve the pain. Hemorrhage is also a serious result. Here saline enemata and rectal oil instillations are employed. In the late and extensive case, a temporary colostomy may be required to relieve the severe pain, hemorrhage and obstruction while the process slowly heals.

Late and serious skin complications have been practically eliminated by the fractional dosage of external radiation after the technics of Coutard. Most of the patients will develop an erythema followed later by tanning or bronzing. Bland oil applications and soothing ointments may be used.

Any anemia should be corrected prior to therapy. Only a very small percentage of patients will show a sensitivity of their blood. Leukopenia should cause concern only when the count falls below 3,000. Temporary interruption of treatment or spacing the treatment over longer periods of time will quickly correct the leukopenia.

The vaginal mucosa routinely develops an epithelitis for which soothing deodorant douches are helpful. Adhesive vaginitis should be prevented by manual and prosthetic dilatations. Real effort is required to maintain an adequate vagina, especially in older patients.

.Bladder sedatives give much relief when mild bladder mucosal irritation occurs during treatment or shortly thereafter. Of the serious bladder complications, ulcerations and telangiectasia may be relieved by fulguration. Twombly and Marshall have recently described a successful combined transvesical and vaginal approach for repair of fistulae. Urologic study should be part of every follow-up procedure. Early recognition of ureteral obstruction and prompt dilatation will prevent a "dead kidney" and increase the salvage of cervical carcinoma.

Infection during the process of irradiation is a most important complication because it is often unavoidable and carries the highest early mortality. External and vaginal irradiation employed before radium applications aid greatly in diminishing and eliminating localized infection. Pyometra can be prevented by maintaining the patency of the cervical canal. The sulfonamides, penicillin and blood transfusions have in some instances controlled the process of parametritis. It is important to differentiate this condition from extension of the carcinoma, as further irradiation would produce a tragic result.

(Radiotherapy has won its present ascendency over radical surgery in the treatment of cervical cancer much less because of any superiority in final results, than in its far greater safety to the patient, and on the point of immediate mortality no one will question its superiority. On the other hand, and in spite of the steady improvement in radiotherapeutic technique, visceral postradiation complications of one sort or another are still disturbingly

thoroughly trained in our own country, has a fine field for missionary work in the Philippines. A public educational campaign modeled after the work of our American Cancer Society should yield a rich reward in the saving of many women's lives.—Ed.)

RADIOGRAPHY AS AN AID TO DOSE-CONTROL IN THE RADIUM TREATMENT OF THE CERVIX

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J. Obst. & Gynaec. Brit. Emp., 54: 137–154, April, 1947

In radiotherapy of cancer of the cervix irradiation should be given in an adequate dose to all of the tumor without causing injury to normal tissues. This is rather difficult to carry out because of the variables involved. Therefore a control is desirable which would show the exact arrangement of the radium and enable one to estimate the distribution of the radiation.

This can be done by radiographic methods as: (a) An anteroposterior and lateral film of the pelvis; (b) Stereoscopic anteroposterior films; (c) A combination of the above plus a mensuration stereoscope in which the tube shift is exaggerated (20 cm.) so that the image shift is easily measurable. This method was carried out on a number of cases at St. Mary's Hospital, London, during 1946 and the results of sample cases charted.

The mechanical radium applicators used were of the Stockholm type. The intrauterine tube contained 2 x 20 mgm. and the vaginal boxes contained 5 x 5 mgm. of radium. The intensity is expressed in roentgens per hour (r/hr.). A total of 6,600 r. given in 3 insertions was considered an adequate dose. Anything smaller than 4,500 r. was regarded as inadequate.

On analyzing the charts and x-ray plates in this study the following points were noted: (1) There was a very rapid decrease of intensity with an increase in distance from the source of radium, e.g., intensity 1 cm. from the vaginal box was 150 r/hr.; at 2 cms. it was 40 r/hr. If the distance was greater than 2.5 cm. the isodoses closely follow circles which are centered in the center of the box. (2) An ideal arrangement of radium was seldom obtained. It necessitated a vaginal vault of 7 cm. width and the dose was estimated along 2 lines extending laterally from the uterine canal at levels one cm. and 2.5 cms. above the level of the external os. The total dose was estimated as the summation of the individual doses. (3) Because of the anatomical configuration of the vagina, cervix, uterus and parametrium, normal tissue was irradiated with from 14 to 16,000 r. which is about as high a dose as normal tissues can stand. (4) Malpositions of the radium are readily recognizable. (5) From an estimation of the dose of radium and the extent of the lesion the amount of supplementary deep x-ray therapy can be recommended with greater accuracy.

little or no value unless physicians make an early and competent diagnosis. The desirability of early diagnosis is self-evident. Experience shows that, even in the so-called early carcinoma where the lesion is seemingly confined to the cervix, the 5-year salvage, when the cases are treated by irradiation, is 50 per cent. If treated surgically, using the Wertheim procedure and selecting cases, a 5-year salvage of 65 per cent is reported. The practice of handling these cases by the ordinary panhysterectomy or total hysterectomy cannot be condemned too strongly.

In order to make a diagnosis, the possibility of malignancy should always be entertained. Irregularities of menstruation just before or during the menopause are significant. Postmenopausal bleeding should be regarded as due to malignancy unless proved otherwise. A pelvic examination with special emphasis on the cervix is imperative. The colposcope or Schiller's test may aid in the diagnosis; biopsy of the cervix is more important when a suspicious lesion is present. Curettage of the endometrium and biopsy of the cervix may be performed if there is a history of menstrual irregularity in a woman of 35 or more, whether or not there is a localized lesion present. In the Department of Gynecology of the Johns Hopkins Hospital, the incidence of very early and unsuspected carcinoma was 2 per cent in cases where biopsy was performed preoperatively as a routine procedure. The vaginal smear method shows promise of some day becoming a simple laboratory procedure, but even with this method, the diagnosis still ultimately depends on the demonstration of carcinoma in curetted material or biopsy of the cervix.

Recently, at Hopkins, Telinde and Galvin furnished incontrovertible proof that cancer starts as an intraepithelial disturbance in the form of basal cell hyperactivity spread throughout the entire fullness of the surface epithelium. It may lie latent for a long time before manifesting invasion. This is exemplified by 2 cases; in the first case $8\frac{1}{2}$ years elapsed between the first manifestation of these intraepithelial changes and the development of frank invasive cancer. In the second case the latent period was 3 years. Telinde and Galvin presented 16 cases in which basal hyperactivity, without invasion evidence in biopsy materials, led them to remove the cervix. In every instance, serial sections of the cervix disclosed very early carcinoma. Their study stresses the importance of biopsy of the cervix.

The writer concludes that this, then, seems to be the clue toward success in the treatment of carcinoma: biopsy of the cervix of any patient 35 years or more, if a lesion is present although this is believed to be a simple erosion; or when irregular vaginal bleeding occurs, even if the cervix appears almost normal. Curettage of the endometrium should accompany biopsy in the latter instance.

(If, as the author states, the 5-year salvage for cancer of the uterus in Manila is only 5 per cent, there is indeed a crying need for the education of Philippine women as to the warning signals of the disease. I presume that the 5 per cent figure applies to cervical cancer rather than to uterine cancer in general, as it would seem difficult to believe that the figure for corporeal cancer would be as low as this, in spite of the lateness at which many cases come under observation. It would seem that the author, who is a progressive young gynecologist

patients had demonstrable recurrence. Twelve patients were well and free of obvious recurrence from 5 to 10 years following operation. Thus, the 5-year salvage rate is approximately 67 per cent.

(The surgical treatment of adenocarcinoma of the corpus uteri has always been a far easier problem than that of cervical carcinoma. In the latter the lymphatic drainage is such that carcinoma cells filter out laterally, sometimes in even early clinical stages, into the parametrium and then into the pelvic lymph nodes, not to speak of the frequent lymphatic permeation into the contiguous vaginal mucosa. The radical Wertheim operation, which took cognizance of this method of spread, was a formidable procedure, and it is not surprising that most gynecologists have been willing enough to give it up in favor of the less hazardous methods of radiotherapy, with its at least definitely comparable results in salvage.

With adenocarcinoma of the body metastasis occurs later, and, what is more important, the extension does not ordinarily involve the surgically difficult area represented by the lower portion of the broad ligament, traversed by that surgical bugbear, the ureter. It is therefore surprising that Warren advocates the Wertheim operation for corporeal carcinoma, if by this he actually means the very extensive procedure indicated by this designation. Most gynecologists would ordinarily content themselves with total hysterectomy and bilateral salpingo-oophorectomy.

It is also rather surprising that Warren emphasizes irradiation only as a postoperative procedure, with no mention of the preoperative irradiation which at the present day is practiced in most clinics, and which, on the basis of present day returns, does seem to improve final results. This is not to say that occasional departures from this plan are culpable, and I myself have not infrequently departed from it. If, for example, one curettes a woman who has had postmenopausal bleeding, and if the gross appearance of the curettings suggests a comparatively early corporeal malignancy, and if this is confirmed by the immediate frozen section diagnosis which is usually possible with a good technician and a good pathologist, I would not hesitate to proceed under the same anesthesia with a radical operation.

On the other hand, in the great majority of cases the disease is not encountered in such an early phase, and there appears to be a genuine advantage in preliminary radiation, which sterilizes the infected and often necrotic cancer area, destroys or devitalizes cancer cells even though not always completely, and probably entraps many of them in the fibrotic reaction produced by the irradiation. These effects are not merely assumed, for they can be demonstrated by the microscopic examination of removed uteri. They constitute a rational basis for the preoperative irradiation in most cases, but the microscopical limitations of such local radiation effects as have been mentioned just as clearly indicate that the irradiation should be followed up, ordinarily about 6 weeks later, with radical removal of the uterus, tubes and ovaries.

The results reported by Warren in his small series appear favorable, although one gets the impression that the statistics might have been too strongly "corrected" by the elimination of certain cases, as mentioned in the last paragraph of the abstract.—Ed.)

(As far as I know, this method has not been used in the radiological clinics of this country, but it would seem to be a worthwhile additional refinement in the avoidance of the injuries of healthy tissues which still occur in the radium therapy of cervical cancer.—Ed.)

CARCINOMA OF THE CORPUS UTERI

K. W. WARREN

Surg. Clin. North America, 27: 696–699, 1947

Early diagnosis of carcinoma of the endometrium should become increasingly frequent with the refinement of newer diagnostic methods and with increasing knowledge on the part of the feminine public regarding the significance of the symptoms of the disease. Radical hysterectomy with removal of the adnexa offers a reasonable prospect of cure in a majority of cases.

The author reviews 33 cases of carcinoma of the corpus uteri from the files of the Lahey Clinic.   Two patients in the group were under 40 years of age, 5 were under 50, 24 were between 50 and 70, and 2 were more than 70 years of age. Postmenopausal vaginal bleeding was the presenting symptom in 82 per cent of the cases; 6 patients complained of irregular menstruation.   Eighteen of the group had borne children.   Although the uterus was enlarged in many instances, reliable signs of malignant disease were present only in the far-advanced cases. The pathologic specimens showed adenocarcinoma in 28 instances and adeno-acanthoma in 5 others.

It is considered at this clinic that one must rely on the radicalness of the surgical procedure for cure and that any beneficial results from irradiation had best be reserved for the postoperative period.   At the clinic, every patient with post-menopausal bleeding or irregular menstruation characterized by abnormal flow who does not respond quickly to conservative measures is subjected to a diagnostic curettage.   An immediate analysis of a frozen section is made, and if carcinoma is found, total hysterectomy after the manner of Wertheim is performed. The detailed features of this technique were recently described by Dr. Lahey. Irradiation is administered following total hysterectomy except in those cases in which histologic analysis reveals the malignancy to be *in situ*.

Of the 33 patients treated at the clinic during the period selected for study, 26 had radical hysterectomy, one had a supravaginal hysterectomy (diagnosis of malignant disease made only by histologic examination of the removed uterus), palliative resection was done in 2 cases, and no operation was performed in 4 cases.   There was one postoperative death, resulting from a cerebrovascular accident on the fifth postoperative day, a mortality of 3.5 per cent.   Twenty-one patients have been traced for 5 years or until obvious recurrence or death from unrelated cause had taken place.   If 3 patients who died within 5 years of treatment and who showed no recurrence before death are eliminated, there are 18 cases upon which to base an estimate of 5-year survival.   Of this number, 6

In evaluating postoperative irradiation, it must be remembered that recurrences are just
as likely, or more so, to occur in distant organs as in the pelvis, since extension is by the
blood stream and not by the lymphatics.—Ed.)

CHORIONEPITHELIOMA: HORMONAL STUDIES AND PATHOLOGICAL FINDINGS

EMANUEL KLEMPNER

*The Gynecological Service and the Laboratories of the Mount Sinai Hospital,
New York, N. Y.*

J. Mt. Sinai Hosp., **14:** 793–797, September–October, 1947 (I. C. Rubin
Anniversary Number)

Chorionepithelioma presents a diagnostic and therapeutic challenge to the
gynecologist. The laboratory investigator is fascinated, and still somewhat per-
plexed, by the biological activity of the tumor. Finally, the pathologist always
finds it a fruitful field for careful study. The following case is reported because
it presents interesting features from the clinical, biological, and pathological
points of view.

History. R. G. was a fifty year old, colored housewife, who had had a normal
pregnancy and uncomplicated delivery at the age of 20 years. She had her
last menstrual period on December 16, 1945. There was no bleeding in January,
1946, but on February 15, 1946, there was profuse vaginal bleeding, marked by
passage of clots. She entered another hospital and there she passed some tissue.
This, as was subsequently reported, was: "Placental tissue," diagnosed on path-
ological examination as hydatidiform mole. She refused surgical intervention
and left that hospital against advice. She continued to bleed intermittently
from February 15 until February 22, 1946, when she was admitted to the Gyne-
cological Service of the Mount Sinai Hospital.

Examination. There was a distinct pallor of the mucous membranes of the
vagina and there was moderate vaginal bleeding. The uterus was soft and en-
larged to the size of a six weeks' gestation. A few irregular prominences could
be palpated on its surface. The cervical canal was patulous and a small poly-
poid structure, the size of a pea, could be seen in the canal. This was removed
and sent to the laboratory for pathological examination.

Laboratory data. Blood: hemoglobin, 46 per cent; red blood cells, 2,600,000
with marked achromia and polychromasia; white blood cells, 11,300 with a
normal differential.

The fragment of tissue removed from the cervical canal was reported: "Single
unusually large fetal villus showing conspicuous Langhans cell proliferation with
many mitoses." The urine pregnancy test was positive. Since this report was
based on the standard rat technique, using 5.0 cc. and 8.0 cc. of urine in the

SARCOMA OF THE UTERUS

N. W. SWINTON AND G. O. MILES

Sarcoma of the uterus is an infrequent malignant tumor comprising 3 to 4 per cent of uterine cancer. It occurs in a ratio of 1 to 40 or 1 to 50 to carcinoma, and is found in 1 to 2 per cent of leiomyomas of the uterus. The diagnosis of sarcoma of the uterus will seldom be made before operation. At any pelvic operation when myomas are encountered, the possibility of sarcoma must be considered. Wheelock and Warren mention the following gross characteristics that should cause suspicion of the presence of sarcoma in a fibroid uterus: (1) Unusual friability of the broad ligament. (2) Unusual vascularity of the tumor. (3) The absence of a sharp line of demarcation between the tumor and the myometrium. (4) The difficulty in shelling out the tumor from its apparent circumscribed limit. (5) The opaque appearance of sarcoma instead of the usual silky, glistening appearance of the leiomyomas. (6) An edematous and partially spiculated appearance of the cut surface which is softer than that of the ordinary fibromyoma. All myomas should be sectioned immediately at the time of operation and histologic study of the tumor made on any suspicion of sarcoma. The treatment of sarcomas of the uterus is surgical. The uterus, cervix, tubes and ovaries and other structures as indicated should be removed. The end results in the treatment of sarcoma of the uterus are favorable, particularly in those arising in myomas.

(The gross characteristics enumerated by the authors as warranting a suspicion of sarcoma seem obvious enough, and yet there is no doubt that they are not familiar to and not observed by many surgeons. Here, as in so many problems arising at the operating table, the gynecologist who knows something of pathology has a very real advantage over one who has not. He will know, for example, that when the cut surface of a myoma is hard and characteristically whorl-like in appearance, there need be little fear of sarcomatous change, but that if it is soft and pultaceous, with perhaps ragged cavity formation, the suspicion should be very strong. He will know, too, that a diffuse sarcoma of the uterine wall may tend to produce nodule-like localizations which should not be mistaken for the more sharply circumscribed myoma. If he has the slightest suspicion, and better as a routine, he will see that myomas are cut into before the abdomen is closed, and that the uterine cavity is likewise laid open. His pathological training will yield worthwhile returns, for he is likely to have a lower incidence of postoperative regrets at not having suspected lesions which are reported by the laboratory, when it may be too late to do much about it.

As the authors state, the treatment of sarcoma of the uterus is usually surgical, although this is partly explained by the fact that the diagnosis in most cases is not made until operation or later laboratory study. This is especially true in the largest group of cases, those in which the sarcoma develops in uterine myoma. Preliminary curettage in such cases is likely to be negative. In cases of endometrial origin, and in some of the diffuse variety, curettage is apt to reveal the lesion. Taken as a group, cases developing in myoma are likely to yield favorable results, but there are not a few exceptions. On the other hand, those arising diffusely in the uterine wall and those of endometrial origin do not as a group yield good results from surgical treatment, either with or without postoperative radiation.

In evaluating postoperative irradiation, it must be remembered that recurrences are just as likely, or more so, to occur in distant organs as in the pelvis, since extension is by the blood stream and not by the lymphatics.—Ed.)

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The fragment of tissue removed from the cervical canal was reported: "Single unusually large fetal villus showing conspicuous Langhans cell proliferation with many mitoses." The urine pregnancy test was positive. Since this report was based on the standard rat technique, using 5.0 cc. and 8.0 cc. of urine in the

test animals, further studies were carried out and it was found that while 1.0 cc. and 0.5 cc. of urine also gave positive results, 0.1 cc. of urine did not evoke a positive response. 8.0 cc. of the patient's spinal fluid was also injected into a 50 gram rat and this, likewise, gave negative result.

Operation. March 2, 1946. Total hysterectomy and bilateral salpingo-oophorectomy was performed.

Pathological report. Specimen is a totally amputated uterus with both adnexa attached. The uterus is moderately enlarged and measures 10.5 cm. in length and 6.4 cm. between the tubal angles. The consistency of the myometrium is softer than usual. The myometrium is 2 cm. thick, has a pale tan color and shows prominent vascular markings. The endometrial cavity is dilated. From the posterior wall and from the left side of the fundus a polypoid tumor mass arises and fills the endometrial cavity. This tumor is markedly hemorrhagic in character, its surface is partially ulcerated and covered with a gray necrotic material. The base of the tumor measures up to 5 cm. in diameter. From its lower edge a pedunculated, soft, polypoid structure which is likewise hemorrhagic, hangs down into the lower portion of the endometrial cavity. The remaining endometrium is thin, pink, and rather smooth.

Posterior course. The patient's convalesence was uneventful; the wound healed by primary union, and she was out of bed on the eighth day after operation.

March 7, 1946 (5 days after operation):

Rat pregnancy test positive with 5.0 cc.

March 14, 1946 (12 days after operation):

Rat pregnancy test positive with 5.0 cc.

Rat pregnancy test negative with 1.0 cc.

Rat pregnancy test negative with 0.5 cc.

March 19, 1946 (17 days after operation):

Rat pregnancy test negative with 10 cc.

Rat pregnancy test negative with 5.0 cc.

Rat pregnancy test negative with 1.0 cc.

The patient has been examined in the Follow-up Clinic and has remained in good health to date. The pelvis is clear, neurological examination has remained normal, x-rays of the chest show no metastases, and repeated pregnancy tests have remained negative.

<center>DISCUSSION</center>

In this case the diagnosis was made on the clinical and the pathological data. The quantitative pregnancy test, although positive, did not exceed the high levels that have been demonstrated in normal early pregnancy. It is worthy of emphasis that the degree of malignancy is not necessarily reflected by the intensity of the pregnancy reaction. This fact has been demonstrated by Frank in his series, who recorded a positive reaction with 0.0025 cc. of urine from a patient with hydatid mole, while a case of chorionepithelioma with metastases required 10.0 cc. of urine to evoke a positive response.

Another point of interest is the belief that the cerebrospinal fluid from patients

with chorionepithelioma produces a positive pregnancy test, whereas in hydatid mole this fluid, rarely, and in normal pregnancy never gives a positive result. The authors have recently encountered a case of hydatid mole in which 8.0 cc. of the cerebrospinal fluid gave a positive pregnancy reaction. The diagnosis cannot be based on one criterion alone but requires the combination of clinical, pathological, and laboratory findings to be certain.

(The description of this case and the illustrations accompanying the paper would seem to justify the diagnosis of chorionepithelioma. It was the clinical and pathological data, and not the biological tests, which made the diagnosis. This should be emphasized, as there are still too many who attach undue diagnostic importance to biological data, such as the persistence of a highly positive test for many weeks or even months after the evacuation of a hydatidiform mole. Such an occurrence does not in itself by any means justify the diagnosis of chorionepithelioma, and most often the latter is not present, though in an occasional case it is.

As in Klempner's case, the hormone levels in chorionepithelioma may be no higher than in normal pregnancy, or, for that matter, the pregnancy test may even be completely negative for considerable periods of time. The microscope is still the final arbiter in the diagnosis of chorionepithelioma, but unfortunately, even the microscopic examination may, in certain cases, offer pitfalls for error, with not infrequent differences of opinion among presumable experts in this field. This fact gives a good opportunity for a plea that all suspicious or even authenticated material relating to hydatidiform mole or chorionepithelioma be sent in, with full clinical data, to the Chorionepithelioma Registry conducted under the sponsorship of the American Association of Obstetricians and Gynecologists.–Ed.)

HODGKIN'S SARCOMA OF UTERUS

HANS N. NAUMANN

From the Department of Pathology, Taunton State Hospital, Taunton, Mass.

Arch. Path., **43**: 324–329, March, 1947

An unusual case of Hodgkin's sarcoma which involved the uterus of an 83 year old white woman is reported. This patient was admitted to the Taunton State Hospital with a diagnosis of senile psychosis. Her course was rather uneventful and two years after admission she died of heart failure.

The salient features of the autopsy were emaciation, an enlarged uterus to the size of a 4 months pregnancy and many fused enlarged lymph glands in the pelvis. The microscopic sections of the fundus and cervix showed tumor cells with marked pleomorphism and Reed Sternberg giant cells characteristic of Hodgkin's sarcoma. It is believed that the process originated in the pelvic nodes and from there invaded the uterus.

In a brief review of the literature the incidence of Hodgkin's sarcoma with uterine involvement was 3.4 per cent (2 cases in 59 and 1 case in 27). The involvement of the genital tract in these cases represents one localization of a

widespread process.   Hodgkin's disease in the very old with uterine involvement is a rarity indeed.

(As the author states, uterine involvement in Hodgkin's disease is rare.   In laboratories of gynecological pathology its incidence is far less than the figure given by the author, simply because it is likely to be encountered as an autopsy finding rather than in the gynecological operating room.   I have recently, through the kindness of Dr. John C. Burch, of Nashville, Tennessee, seen a section of cervical tissue obtained in the operating room, concerning which there was some disagreement of opinion, but in which several nationally known general pathologists diagnosed Hodgkin's disease.   Unfortunately I do not as yet know whether there was any other evidence of Hodgkin's disease in this patient.-Ed.)

THE ADNEXA

CANCER OF THE OVARY

N. W. SWINTON AND C. R. YANCEY

Malignant tumors of the ovary comprise approximately 4 per cent of malignant disease found in women. The authors have reviewed 64 cases of ovarian cancer on which they have complete data at this time, and also have reviewed the recent literature on the subject.

Characteristically, ovarian cancer does not cause early symptoms. An abdominal enlargement, lower abdominal pain and disturbances of menstruation are the common symptoms noted. The importance of the premalignant, benign neoplastic ovarian tumors, that is the papillary cystadenomas, must be appreciated and the tumors removed when found. Unfortunately, the papillary cystadenomas also do not present characteristic early symptoms. Because of the absence of early symptoms and the potentially malignant ovarian tumors, the importance of routine pelvic examinations in women during the childbearing and postmenopausal ages cannot be too strongly emphasized. All solid ovarian tumors should be regarded as potentilly malignant.

The establishment of a diagnosis of ovarian malignancy or potential ovarian malignancy will depend on the detection of ovarian cancer and the papillary cystadenoma at the time of operation in the majority of cases. When a solid ovarian tumor is encountered at operation, careful inspection and palpation of both ovaries and adjacent structures must be made. Following the removal of such a tumor, it should be sectioned immediately and histologic examination made at once if there is any suspicion of cancer.

When ovarian cancer is diagnosed at operation, as radical an approach to this form of malignancy must be made as to cancer in any other region of the body. Both tubes and ovaries, uterus and cervix and, when indicated, adjacent structures such as the omentum must be removed. In the removal of ovarian tumors, the importance of avoiding spilling of the contents, and the careful search for implants and metastases in the abdominal cavity must be appreciated.

Intensive deep radiation therapy should be given to these patients postoperatively.

With the establishment of an early diagnosis of carcinoma of the ovary, with radical removal of these tumors and with the use of deep radiation therapy, the end results should be reasonably good and the 5-year survival rate approach that of carcinoma of the breast and carcinoma of the colon and rectum.

(The treatment of ovarian cancer presents an even more depressing picture than that of uterine, and especially cervical, cancer. Fortunately it is not nearly as common a lesion

though certainly anything but rare. With the uterine forms of cancer, there has been at least some improvement in results over the years, and there is justifiable hope that even without any spectacular additions to our therapeutic armamentarium, our results can be steadily improved by educational methods which will bring to treatment a steadily increasing proportion of the favorable early stages of the disease.

In the case of ovarian cancer, on the other hand, one rarely and only accidentally encounters a really early case in a stage in which radical operation might be expected to result in cure. I do not recall any report of a large series of such early cases, but such a study would be of great value. It might be expected to show that the present highly unfavorable results in the treatment of ovarian cancer are less indicative of an innately higher degree of malignancy than they are of the fact that most cases which come to operation represent late stages, as they undoubtedly do. In these comments I am not including the relatively uncommon dysontogenetic tumors in which the degree of malignancy is definitely less than it is in the common or garden varieties.

In the case of uterine cancer, our educational campaigns warn women of the possible significance of abnormal bleeding or discharge. But what shall we warn them about in connection with ovarian cancer? Not bleeding, for ordinarily there is none; not pain, for this is usually absent; not of lumps in the lower abdomen, for when these are felt by the patient her golden moment has passed. I know of only one admonition which can be considered protective in so far as this disease is concerned, and that is that all women should submit to periodic examination, preferably at 6 monthly intervals, especially after the age of 35. Such propaganda is sure to be of only fractional value, as the vast majority of women will not, in the foreseeable future, cooperate in such a program, which should of course be only a part of such a general cancer detection program as the one now being carried on under the auspices of the American Cancer Society. But the number of women who seek such protective examinations is steadily increasing, and there is a justifiable hope that this increase will be reflected in better cure rates.

The finding of a definite ovarian neoplasm should, generally speaking, constitute valid indication for operation. I say "definite ovarian neoplasm" advisedly because, as everyone knows, certain functional cysts of the ovary may be large enough to simulate genuine neoplasms. However, the distinction can usually be made by observing the behavior of such ovarian enlargements for a short time, and the delay involved is not likely to be hazardous to the patient. Once the gynecologist is sure in his mind that the ovarian mass is a neoplasm, its removal should be advised even though the patient is free of symptoms.

In ovarian tumors of the cystic variety there is an ever-present hazard of either existing or subsequent malignancy. In this respect they differ from uterine fibroids, in which malignant change is relatively rare, and in which in many cases non-surgical management is often entirely justifiable. Again, if the examiner finds what he takes to be a solid tumor of the ovary, he cannot be sure that it is not malignant and its removal is indicated.

It is especially in this field of surgery that the gynecologist who is also a good pathologist has a genuine advantage over one who is not. If he finds a solid tumor he can often be pretty sure that he is dealing with a benign fibroma or Brenner tumor and not a solid type of carcinoma or a sarcoma. He can often, though not always, intelligently evaluate the potentialities of serous papillary cysts, often justifying conservative operation in young women in whom later pregnancy is highly desired, in other cases impelling him to radical operation even in young women, and in all women in whom the preservation of the reproductive function is not important. All sorts of problems may arise, and the decision as to the proper treatment must be based on very individual factors. Not even the most highly trained gynecological pathologist will avoid some mistakes, but no one will argue that a reasonable competence in the living pathology observed at the operating table is not an asset well worth acquiring.–Ed.)

BILATERAL ARRHENOBLASTOMA WITHOUT MASCULINIZATION, ADENOMA TESTICULARE OF PICK

MINNIE B. GOLDBERG AND ALICE F. MAXWELL

San Francisco

The authors report the case of a 19-year-old girl who presented the paradoxical picture of primary amenorrhea, tall eunuchoid build, *large breasts*, poorly developed external genitalia with rudimentary vagina, congenital absence of uterus and cervix, absent axillary and scant pubic hair and a high urinary gonadotropin titer. The adnexa were not palpable.

Surgical exploration of the pelvis prior to performing a vaginal plastic operation revealed bilateral, poorly developed gonadal structures composed of tissue grossly resembling adrenal cortex. This, on microscopic examination, proved to be a highly differentiated type of arrhenoblastoma. Careful search revealed no evidence of ovarian tissue. Both tumors were removed. Bilateral rudimentary structures suggesting the unfused anlage of uterus were also demonstrated.

The source of the estrogens responsible for the breast development remains a mystery. This case brings up many interesting questions concerning sex determination and differentiation.

(It is in just this highly differentiated variety of arrhenoblastoma, the adenoma testiculare described by Ludwig Pick as far back as 1904, that one is most likely to note an absence of masculinization symptoms, in spite of the fact that it is in these that the histological structure approaches that of normal testicular tissue much more nearly than in the undifferentiated and intermediate forms. Only about one-third of the reported cases of adenoma testiculare have been associated with evidences of masculinization. It is curious, and not easy to explain, why the cells of the undifferentiated group should show so much more capacity to produce the androgenic hormone than the ripe variety.–Ed.)

FEMALE UROLOGY

SURGICAL CURE OF URINARY INCONTINENCE IN WOMEN

R. W. Te Linde

The Gynecological Department of the Johns Hopkins Hospital and University, Baltimore, Maryland

Because urinary incontinence in women is a common and distressing complaint and since the surgical results are not as good as they should be, the experience in this subject at the Johns Hopkins Hospital, covering the past 10 years, has been reviewed.

The more common types of incontinence are: (1) Stress incontinence, the most frequent type, is either partial or complete and usually is associated with cysto-urethrocele and prolapse; (2) Vesicovaginal fistulae. They are the result of surgical and childbirth injuries, malignancy, or lymphopathia venereum; (3) Defects in the urethra and sphincters. These may be due to obstetrical and surgical accidents or to congenital defects; (4) Incontinence due to neurologic disease; (5) Ureterovaginal fistulae, resulting from operative or irradiation injuries; (6) Inflammatory lesions of the urinary tract causing enough urgency and frequency to simulate incontinence are not classified as a type of incontinence but are mentioned so that the differential diagnosis is considered and surgery not done.

The principal causes of stress incontinence are: (1) A sagging of the urethra and base of the bladder preventing the urethral sphincters from closing (frequently the mechanism in cystocele); (2) A decreased sphincter muscle tone occurring with advancing years; (3) A formation of scar tissue in the periurethral region preventing the sphincters from closing (from childbirth or previous operations).

The usual surgical treatment of stress incontinence is plication of the vesical sphincter and the reunion of the pubovesicocervical fascia beneath the urethra and base of the bladder. Kelly was the first to devise this method of repair. Kennedy noted the presence of sphincters along the entire urethra, showed that periurethral adhesions were a factor in incontinence, and devised an operation to correct this. At present the operation done most often by Dr. Te Linde combines some of the features of the Kelly and Kennedy operation depending upon the pathology present. In those cases associated with urethrocele or cysto-urethrocele, the entire urethra and sphincter region is plicated with mattress sutures of medium silk, a second row of catgut being placed through the fascia. In cases where the sphincter fibers are destroyed or scarred from previous childbirth or operative injury without urethrocele or cystocele present, a more extensive dissection around the circumference of the urethra is carried out before plication. In those cases occurring in nulliparous women who have a normal

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innervation to the bladder the urethral sphincter is plicated for its entire length. During the previous 10 years 249 of these operations were done with 90 per cent being reported as well and 5 per cent improved.

In certain carefully selected patients the Goebell-Frangenheim-Stoeckel operation is used to cure stress incontinence. The indications for this operation fall into 3 groups: (1) Those cases in which previous unsuccessful plications have resulted in considerable scar tissue; (2) those in which the urethra and sphincter mechanism have been destroyed and the reconstructed urethra has no contractile power; (3) and selected cases of neurologic bladders (those in which there is relaxation of the involuntary sphincter and an absence of voluntary sphincter control in a bladder which is not too spastic).

The Aldridge modification of the Goebell-Stoeckel has been generally used in this clinic since 1942. Briefly this operation is carried out as follows. The lower abdominal fascia is exposed by a transverse incision, strips of fascia are cut on either side long enough to be carried down retropubically and encircle the urethra. After a midline incision through the anterior vaginal mucosa and the fascia stripped back from the flaps the previously developed fascial strips from the abdomen are brought down retropubically with a long Kelly clamp, over-lapped, and sutured. This general type of operation has been done 13 times during the past 10 years with 4 failures, one of which was attributable to a great excess of scar tissue. The other 3 were done on patients who had had artificial urethra made. The factors involved in these 3 failures were: (a) absence of any normal sphincter mechanisms, (b) inadequate length and depth of the artificial urethra, and (c) poor blood supply due to chronic edema and fibrosis of an underlying disease process.

Vesicovaginal fistulae result chiefly from total abdominal hysterectomies and vaginal deliveries. Of the 41 cases reported there were 15 due to the former and 8 to the latter. The remainder were due to vaginal removal of cervical stumps, radium treatment of carcinoma of the cervix, subtotal hysterectomy, rupture of the uterus, bladder and vagina following pituitrin during labor, Manchester operation, colpotomy, cesarean section, automobile accident and biopsy of a bladder tumor. Prophylaxis therefore plays an important role in the treatment of vesicovaginal fistulae.

Besides good surgical judgment and improvisation, the important principles in vesicovaginal fistulae surgery are as follows: (1) 6 months should elapse after the occurrence of a fistula before a repair is attempted. The tissues then will be in as good condition as possible. (2) Good exposure is essential. The approach of choice is vaginal. Occasionally Schuchardt's incision may be used to advantage. (3) The Latzko principle of partial colpocleisis for closure of a fistula should be kept in mind as a relatively simple procedure in difficult cases. (4) The vaginal mucosa should be widely denuded, the defect closed by a line of interrupted Cushing sutures of fine catgut without tension, bladder tested for leakage with sterilized milk, and a second line of sutures is used if tension is not great. Then the vaginal mucosa is approximated with silver wire mattress sutures. (5) Drainage of the bladder should be insured not only with an indwelling urethral catheter

but by an additional vaginal or suprapubic cystotomy. The cure rate in this series of 41 patients was 90 per cent.

The most difficult cases of incontinence to cure surgically are those resulting from complete destruction or congenital absence of the urethra. A plastic operation for the construction of a urethra in cases such as these has been described by the author.

Ureterovaginal fistulae usually result from operative injury to the ureter. If the ureter is cut and not recognized, incontinence usually develops immediately. If the ureter is crushed, ligated, or has its blood supply interfered with incontinence usually develops after several days. Differential diagnosis from vesicovaginal fistulae is made by placing methylene blue solution in the bladder and by cystoscopy. Kidney status and function is evaluated by a differential P.S.P. test and intravenous pyelograms.

The surgical cure for ureterovaginal fistulae is uretero-ureteral anastomosis, implantation of a ureter into the bladder, or nephrectomy. The time to do the operation requires the keenest surgical judgment. The type of procedure to be carried out can be decided on at the time of operation and will depend largely on the status of the pelvic viscera and the location of the fistula. Whichever procedure is selected, it is well to have the ureter catheterized first and if infection is present have the patient on sulfonamides.

(In this comprehensive review the author formulates very clearly the various types of urinary incontinence and their causes, and presents a sound discussion as to the management of these various groups. The great majority of cases of stress incontinence, as he says, are amenable to comparatively simple procedures, usually of the Kennedy type, with or without the Kelly procedure of vesical plication. The fact remains, however, that in at least a small group of cases, these simpler procedures are unsuccessful, so that occasional resort must be made to the fascial sling procedure of Goebell-Stoeckel or some modification thereof. Both Aldridge and Studdiford have described such procedures, and they both appear to offer definite advantages.

As for vesicovaginal fistulas, here again one must adapt the procedure to the position and size of the opening. Even fistulas at the vaginal vault can often be satisfactorily exteriorized by the Schuchardt incision and satisfactorily closed, though there may be an occasional exception in which the Latzko procedure may have to be resorted to. For more easily accessible fistulas the Simms procedure, perhaps preferably employing silver wire rather than the catgut which many now use, gives excellent results. On the other hand, especially in the fistulas of larger size, very satisfactory results are almost always attainable by dissecting the bladder freely from the vaginal mucosa, thus mobilizing the bladder flap and making closure of the bladder wound easily possible with no tension whatever. Fine catgut, preferably in interrupted sutures which turn in the bladder wall without penetrating into the organ, give excellent results. If the vaginal wound can be closed in such a way that the vaginal line of sutures does not immediately overlie that in the bladder, as is almost always possible, this is certainly desirable. See also following abstract of article by Sjövall.—Ed.)

A MODIFICATION OF THE PLASTIC OPERATION ON THE PYRAMIDALIS FASCIA IN URINARY INCONTINENCE. OPERATION BY THE ABDOMINAL ROUTE ONLY; REPORT ON THREE CASES

A. SJÖVALL

University Clinic of Obstetrics and Gynecology, Lund, Sweden

Sunde, in 1943, published a modification of the pyramidalis fascia operation of Goebbel-Stoeckel for incontinence of urine in women. In this modification, the fascia flap is not split, but is drawn in a single loop through the urogenital diaphragm around the urethra, elevating the vesical neck. The fascia flap is sewn to its point of origin above the symphysis. Thus, the drawbacks attending the splitting of the flap into halves are avoided. In Sunde's technic no sutures at all are placed under the vesical neck, minimizing the risk of infection from the vaginal incision. In order to eliminate entirely this source of infection, Sjövall has operated upon 3 patients by the abdominal route only.

Except that the operation is carried out by the abdominal route, the technic of Sunde is followed. The vaginal wall is separated from the urethra by means of fluid infiltration, 40 cm. of an ordinary etocainepinephrine solution being injected from below. From the abdominal wound the endopelvic fascia is incised on both sides of the urethra. With a very curved forceps a single, unslit flap of the pyramidalis fascia (according to Sunde) is led through the urogenital diaphragm around the urethra between this structure and the vaginal wall. The end of the flap is sewn to its origin above the symphysis; the fascia ring is completed.

This operation eliminates the risk of infection, always to be feared when a vaginal incision and manipulations from a vaginal wound are carried out.

The abdominal technic is suitable in cases where the pyramidalis fascia operation would otherwise be indicated. In cases of severe incontinence with a narrow vagina and impossibility to pull down the portio, the operation from an abdominal incision only is a most convenient procedure. The author presents 3 cases which have been operated upon by the technic described in this paper. The results have been excellent with perfect continence.

(No illustrations are published with this paper, but I believe that the description is sufficiently clear to permit of its visualization. It represents a modification of the Sunde procedure, which in itself is a modification, though a rather sharp one, of the Goebell-Stoeckel fascia sling operation. Theoretically one would think that the dissection of the endopelvic fascia from above would not be easy, though it might conceivably be easier than the vaginal approach in patients with, as the author states, a very narrow vagina and a high fixed cervix. In spite of what would seem to be a definite advantage in the utilization of an unsplit fascial loop, I would be inclined to question whether the results would be better than with the Aldridge or Studdiford modifications of the Goebell-Stoeckel operation. See also preceding abstract of paper by Te Linde.—Ed.)

AN EXTRAVAGINAL TECHNIC IN THE OPERATION FOR URETHRO-VAGINAL AND VESICO-VAGINAL FISTULAS

A. INGELMAN-SUNDBERG

Women's Clinic Karolinska Sjukhuset, Stockholm

This author previously worked out an operation for urinary incontinence, whereby the pelvic floor is repaired after a dissection which has freed the entire anterior vaginal wall, this having been done through an incision under the urethra. In this way, both the urethra and the base of the bladder are freed and the anatomical structures are easy to review. It is natural that a similar technic should be used for other operations on the bladder and urethra, especially in urethrovaginal and vesicovaginal fistulas. Thus, the author describes an extravaginal method for the correction of such fistulas. The technic is briefly as follows:

A triangular flap of the mucosa is dissected loose in such a manner that the apex is near the·clitoris and the base just above the vaginal introitus. A sleeve of mucous membrane is left around the urethral orifice. At the base of the triangle, the incision is extended laterally so that the entire anterior vaginal wall can be dissected loose. This dissection is carried out close to the vaginal mucosa with a soft catheter placed in the urethra. When the fistula is reached it is isolated and severed close to the vaginal mucosa. The dissection is continued until the urethra and bladder floor have been freed. The.fistula is then invaginated and a row of sutures placed outside of this. The defect in the vaginal wall is sutured with interrupted stitches. The pubocervical ligaments are freed and sewn together under the bladder floor and fixed to the cervix. The levator ani muscles are then freed toward the symphysis by blunt dissection. If anatomical conditions permit, the anterior portions of the levators can be sewn together in the midline. However, should too much tension be produced or the introitus become too narrow, the levators may be divided so that there are 2 anterior portions attached to the symphysis and 2 posterior parts attached in the region of the coccyx. The anterior portions are sewn together under the bladder neck. If further interposition is desirable, the anterior portions of the bulbocavernosus are freed and sewn together as in the operation devised by Martius. Next, the posterior levator portions are located through an incision in the posterior vaginal wall and are united in the midline in front of the rectum. Following placement of a rubber drain in each ischiorectal fossa, redundant tissue is trimmed away and the mucosa is sutured.

This operation offers the following advantages over methods usually employed: (1) better view of the anatomy; (2) thorough invagination of the fistula is possible because the bladder is exposed; (3) strong interposition of soft parts is obtained between vagina and bladder; (4) the incision in the bladder wall is not located in

the same place as the defect in the vaginal wall; and (5) through the plastic repair of the bladder floor and elevation of the bladder neck, most likely the risk of secondary incontinence is minimized.

Thus far, the author has used this method in 3 cases, all with good results. One of these patients had been operated on twice for a bladder fistula. Another patient had large diverticulae in the uppermost portion of the urethra causing urinary incontinence. 6 figures.

(I am not sure that a clear idea of this operation can be easily obtained from the above description, full though it is, in the absence of illustrations, but it did not seem practicable to get these without undue delay in the publication of the abstract. For the most part, the operation would seem to be about that which most of us would select in the repair of such fistulas, stressing the principle of free mobilization of the urethra or bladder, or both. The additional feature suggested by the author, and the debatable one, is that of utilization of the levatores ani in the manner which he describes. Aside from appearing to be unnecessary, the objections which would occur to most of us would be those mentioned by the author himself, i.e., the tension involved and the narrowing of the introitus which might result. —Ed.)

OPERATIVE GYNECOLOGY

SYMPATHECTOMY FOR THE RELIEF OF PELVIC PAIN IN WOMEN

J. P. GREENHILL

Chicago, Illinois

In this paper the author discusses only that type of pelvic pain the origin of which is either unknown or, if known, its cause cannot or should not be removed surgically. In this category he includes the following types of pain: (1) severe dysmenorrhea, (2) endometriosis in young women, (3) inoperable carcinoma of the female genitals and (4) pelvic pain of unknown origin unsuccessfully treated by one or more laparotomies.

Because the site of the foregoing types of pain cannot be removed, some other method of relieving the pain must be employed in these cases. Drugs, chiefly the analgesics and opium derivatives, are generally given but they are unsatisfactory because they relieve pain for only a few hours at a time. Endocrinotherapy, physiotherapy and even roentgenotherapy are likewise of little or no help. A method of treatment which is highly successful in all of these cases is removal of the pelvic sympathetic plexus. This operation is known under a variety of names such as pelvic sympathectomy, pelvic neurectomy, resection of the presacral nerve and resection of the superior hypogastric plexus. The operation is relatively simple and may be performed by anyone trained to do abdominal surgery.

Severe dysmenorrhea. Dysmenorrhea is generally divided into primary and secondary types. The secondary type is associated with a pathologic disturbance in the pelvis such as endometriosis, uterine fibromyomas, inflammatory disease or stenosis of the cervix from injudicious cauterization or other causes. The menstrual pain can be relieved by surgically removing the pathologic condition. On the other hand, primary dysmenorrhea is not associated with any detectable abnormality in the pelvic organs and because of this its treatment is most unsatisfactory. There is no unanimity of opinion concerning the cause of severe primary dysmenorrhea. Undoubtedly there is more than one etiologic factor. Since the cause of the pain is unknown the treatment is empiric. Chief reliance is placed on analgesic drugs, atropine sulfate and the endocrines. None of these is uniformly successful and thus after medication fails, physical means, such as dilatation of the cervix, with or without curettage and with or without the insertion of a stem pessary into the cervical canal, are usually employed. These procedures also are unsatisfactory because when they are effective the benefit is nearly always temporary. On the other hand pelvic sympathectomy

is almost permanently 100 per cent successful in severe dysmenorrhea. However, no girl or woman should be subjected to pelvic sympathectomy until all conservative measures have been tried over a sufficiently long period of time. In most instances of primary dysmenorrhea there is a large psychic factor and this must be considered while the conservative measures are being used.

Endometriosis in young women. It is well known that endometriosis produces pain as long as estrogen stimulations exist. Therefore the simple way to relieve such pain is to remove both ovaries or destroy ovarian activity by radiation therapy. This treatment is proper in women more than 40 years of age but not in young women. In the latter every effort should be made to conserve normal ovarian tissue, preferably by retaining an intact healthy ovary if one is present. If both ovaries are endometriotic as much healthy ovarian tissue as possible should be preserved. Following such conservative operations many women remain well without any further treatment. Others, however, continue to have periodic pain just before and during the menstrual periods. Because of this the author believes that whenever a conservative operation is performed for endometriosis a pelvic sympathectomy should be done at the same time.

Carcinoma of the uterus. Carcinoma of the uterine cervix is one of the most serious afflictions that can develop in a woman because at least three out of every four women so afflicted die from it as do about half of the women with cancer of the body uterus. Furthermore, nearly all such women suffer excruciating pain during the latter part of their lives and in a large proportion of them the almost unbearable pain is constantly present. Pelvic sympathectomy should be done at the time of a Wertheim operation as it requires only a few extra minutes to perform and the consequent benefits to the patient, should there be a recurrence, are manifold. Likewise in all cases when an abdominal operation is performed for carcinoma of the body of the uterus, tubes or ovaries, a pelvic sympathectomy should be performed prophylactically to prevent pain in the event of recurrences. In extensive cancer of the genitals for which a laparotomy is not performed, the severe pain can be relieved much more simply, economically and safely by intraspinal injection of alcohol than by pelvic sympathectomy.

Pelvic pain of unknown origin. Occasionally women are seen who complain of more or less constant pain, who were subjected to one or more laparotomies without relief and who are called hypochondriacs or neurotics. Most of these women first have their appendix removed, then they are subjected to one or more subsequent laparotomies for ovarian cysts, adhesions and other causes and still their pain persists. In such women a pelvic sympathectomy, even if the source of their pain cannot be ascertained, will result in dramatic relief.

The operation described is the one recommended by Cotte. (See next abstract.) Since many of the patients for whom this type of operation is indicated are poor surgical risks, it is best to open the abdomen under direct infiltration anesthesia. The anatomy, physiology and technic of pelvic sympathectomy are discussed.

(The author wisely states that pelvic sympathectomy should not be done unless all the more conservative measures have failed, but it is doubtful as to whether this restriction of

indication is as generally followed as it should be.   The 4 chief indications, as given by the author, are about those which would be considered valid by most gynecologists.   It will be seen that the operation is indicated, not only in a proportion of the severe dysmenorrhea of purely primary type, but also as an auxiliary measure in operations performed primarily for some definite surgical indication, such as endometriosis or marked retroflexion.   The correction or removal of such pathology may or may not in itself relieve the dysmenorrhea, and it is often wise to reinforce the original procedure with a sympathectomy.   Personally, I have done more sympathectomies in this combined fashion than for primary dysmenorrhea per se.   The author does not give statistics or follow-up studies, but makes the statement that almost 100 per cent of patients are permanently relieved.   This figure is far greater than that generally given, most authors putting it at from 60 to 70 per cent of successes. See also following abstract of paper by Phaneuf.—Ed.)

PRESACRAL NEURECTOMY IN INTRACTABLE DYSMENORRHEA

Louis E. Phaneuf

Boston, Massachusetts

The purpose of this paper is to report the results of presacral neurectomy for intractable dysmenorrhea, performed on 76 patients from December 4, 1933 to June 21, 1946.   It is in primary dysmenorrhea of the intractable type that presacral neurectomy or resection of the superior hypogastric plexus finds its greatest field of usefulness.   The results in a number of cases are dramatic, and young women who had previously been crippled each month by a dysmenorrhea that necessitated their remaining in bed one or more days may menstruate without pain after this intervention.   This operation should, however, be resorted to, only in those cases in which all other simpler methods have failed, and should be reserved for the so-called "spastic" or uterine form of dysmenorrhea, a condition in which the patient experiences severe cramps.   It is not intended for ovarian dysmenorrhea, since it has but little value in that condition.   Although striking results are obtained in the control of menstrual pain by presacral neurectomy, one should refrain from applying it to women who may be relieved by the simpler forms of therapy.

TECHNIC OF PRESACRAL NEURECTOMY AS PROPOSED BY COTTE

In the Cotte operation, the patient, under suitable anesthesia, the bladder having been emptied and the abdominal wall prepared, is placed in the Trendelenburg position.   Cotte advises an abdominal incision partly above and partly below the umbilicus.   Unless the patient is very obese the author prefers the median pelvic incision, drawing the upper end of the incision upward by a suitable retractor.   The intestinal mass is pushed upward and held by laparotomy pads, and the sigmoid is packed to the left with suitable pads, thus ex-

posing the inter-iliac triangle. The peritoneum is opened in a superficial manner and is separated from the underlying areolar tissue (the cellulofibrous membrane of Cotte) before it is incised. This layer of areolar connective tissue contains the sympathetic fibers and ganglia that make up the superior hypogastric plexus. The so-called cellulofibrous membrane is dissected from side to side and bunched toward the middle. (The author has found the delicate Metzenbaum scissors to be an excellent instrument for this dissection.) In the course of this dissection the bifurcation of the aorta, the right common iliac artery and its bifurcation into the external iliac artery and the hypogastric artery, and the right ureter are exposed. On the left side the large common iliac vein is in evidence. The bundle or areolar tissue containing the sympathetic nerve elements is ligated 1 cm. above the bifurcation of the aorta and resected, the lower part of the resection being carried out considerably below the promontory of the sacrum, with the middle sacral exposed. The fasciculus of areolar tissue containing the nerve elements is resected to the length of 4 to 6 cm.

<div style="text-align:center">RESULTS</div>

In this series of 76 patients, the ages ranged from 13 to 38 years. Fifteen patients were between 13 and 19 years old, 45 between 20 and 29, and 16 between 30 and 38. The results which are based on the patients' voluntary reports, have been classified as satisfactory, improved and unimproved. The satisfactory cases were those in which pain following the operation was absent or barely noticeable. The improved cases were those in which the patients had pain for a short time but considered themselves greatly relieved. The unimproved cases were those in which there was as much pain subsequent to the operation as there had been before it. Follow-up was obtained in 68 patients (90 per cent), of whom 52 were examined in the office and 16 answered questionnaires. Of these patients, 40 (59 per cent) had satisfactory results, 19 (28 per cent) were improved, 8 (12 per cent) were unimproved, and 1 died during the operation; another had one pelvic delivery, and a third had a transverse cervical section.

In the single case with a fatal termination, Case No. 33, the patient was a girl 13 years of age, whose physical development corresponded to that of a young adult. Her dysmenorrhea was so severe that she had been incapacitated each month. She had been given analgesics and hormones without benefit, and she had had a previous dilatation and curettage by another surgeon, without relief. She was operated on under general anesthesia. When the abdomen was opened, the omentum and sigmoid were found to be adherent to the posterior surface of the fundus of the uterus. It was believed that the uterus had been perforated at the time of the dilatation and curettage, resulting in these adhesions. A presacral neurectomy was performed without any special difficulty. As the posterior peritoneum was being closed the patient expired. The death was classified as due to anesthesia.

(Like Greenhill (see preceding abstract), Phaneuf urges that this operation be done only if all simpler and safer methods have failed. Like any other abdominal procedure, it is not

completely without risk, as attested by Phaneuf's report of óne fatal case in his series of 76. The fact that this sort of surgical or anesthetic accident can occur even in the hands of such a highly trained and experienced gynecologist as Phaneuf only serves to illustrate the inevitable even if very slight hazard of sympathectomy or any other surgical operation. The results reported by Phaneuf are more in keeping with those reported by most gynecologists than are those given by Greenhill.—Ed.)

A NOTE ON FOTHERGILL'S COLPORRHAPHY

C. P. BRENTNALL

St. Mary's Hospitals, Manchester, England

The purpose of this paper is to review the history of vaginal plastic operations for the cure of genital prolapse during the past 80 years and place the credit and value of Fothergill's colporrhaphy in its rightful place.

The first plastic operation for prolapse was performed in London about 1831 by Mr. Heming. In this case a cure was brought about by "artificial contraction of the vagina." For the next 70 years the object of plastic operations was to narrow the vagina to obtain cure. There was Huguier of Paris who in the 1840's performed an amputation of the cervix in every case of uterine prolapse. In the 1850's Baker Brown of London did a radical perineal operation for prolapse which narrowed the vagina to a marked degree. Again in the 1860's Marion Sims of London devised many vaginal plastic operations for the relief of prolapse but the object of cure still remained narrowing of the vagina. His operation obtained narrowing higher up the canal than could be done by perineal operations and combined cervical amputation and perineorrhaphy as indicated. Hegar in the 1870's did a rather extensive operation in one or two stages which amounted to an amputation of the cervix, anterior and posterior repair, then perineorrhaphy. During the ensuing 30 years many variations of vaginal plastic operations were devised and repaired, but none seemed to appreciate the anatomical basis for the proper cure of uterine prolapse. All depended on narrowing of the vagina.

In 1907 Fothergill published articles on the anatomy of the female pelvis and a description of an anterior colporrhaphy which utilized the transverse ligaments of the cervix by reefing them in front of the cervix. In 1908 Donald also published an article on the cure of uterine prolapse but no deep sutures were used and nothing was different from many of the previous operations which depended on narrowing of the vagina to effect cure.

In 1913 Fothergill reported the details of his final operation as it is known today. It was based on a solid knowledge of the anatomy of the female pelvis and used the cardinal ligaments of the cervix in the repair.

(This paper will be of interest to everyone who is anxious to know something about the development of the operative treatment of genital prolapse, and especially the important contributions emanating from the Manchester school of gynecologists.—Ed.)

AVOIDANCE OF CATHETERIZATION FOLLOWING VAGINAL PLASTIC OPERATIONS

ARTHUR A. GEMMELL

Department of Obstetrics and Gynecology, University of Liverpool

Following vaginal plastic operations many patients have great difficulty in voiding spontaneously which necessitates repeated catheterizations or an indwelling catheter. To reduce the catheterization rate the Mayo Clinic group instilled one ounce of 0.5 per cent mercurochrome into the bladder following pelvic operations and reported considerable success.

The author tried this technique of bladder instillation in 63 cases of prolapse and used 50 previous cases who did not receive mercurochrome as controls. This preliminary report showed that 72 per cent of the cases without mercurochrome had to be catheterized while in only 9.5 per cent with the bladder instillation was catheterization necessary.

The suggested action of this drug is that of an irritant and that this action has a greater effect upon the nervous control of the bladder than has the inhibitory of the pain or tissue damage in the area of operation.

Two cases during this study had hematuria following mercurochrome. This was thought to support the idea of its irritant action.

(Gynecologists still differ as to the advisability or inadvisability of using indwelling catheters after vaginal plastic operations. In my experience, catheterization is not usually necessary in the simpler operations on the posterior wall, and its necessity is lessened by mercurochrome injections, as recommended by the author. On the other hand, I do not think that this will prevent difficulty in voiding in the case of the more extensive anterior wall procedures, such as the various operations, usually of Manchester type, for cystocele or prolapse. In such cases I prefer a retention catheter for several days. After removal of the catheter, daily instillations of mercurochrome are used after the catheterization which is done daily for a few days to make sure that there is not a lot of residual urine. In some cases, however, it may be necessary to replace the indwelling catheter for a number of additional days.

A not unimportant consideration in the use of a retention catheter after operation of the above mentioned type is that there is frequently some retraction of the urethra, so that catheterization may be rather difficult to even an experienced nurse. The patient hates to be "poked at," as she sometimes puts it, at regular intervals when she is still sore and hypersensitive, and this difficulty is obviated by the indwelling catheter.

There are of course all sorts of individual variations in the management of these cases, so highly successful as a group in their ultimate results, but requiring such meticulous after-care, especially as regards the bladder. While the above represents my reaction to the problem at the moment, I have no doubt it will change from time to time in the future, as it has in the past, and this appears to be the case with all my gynecological friends as well. —Ed.)

STERILITY IN THE FEMALE

N. F. Miller

Ann Arbor, Michigan

J. Michigan M. Soc., 46: 812, 1947

The problem of sterility requires a comprehensive and methodical study. It usually is not difficult to evaluate the part the husband may play in a nonfertile union. Discovering the cause of infertility in the woman may be difficult and therefore it is well to approach the problem in a logical way. The simpler studies are carried out first except in those patients where there is abundant reason to believe that nonpatency of the tubes is the primary cause of failure to conceive. The customary procedures carried out at the University of Michigan Hospital for infertile patients are covered in this presentation.

(As the author states, it is ordinarily much easier to evaluate the husband's role in a nonfertile union than that of the wife. The most important first step is of course examination of the semen. In specimens which are perfectly normal, this is often reasonably certain from a mere glance under the microscope, but there are degrees of inadequacy, of both count and morphology, which cannot always be evaluated with sharp precision as weighed against corresponding degrees of at least relative infertility which may be revealed in the wife. Since success or failure depends on a summation of both masculine and feminine factors, the proper working rule is to do all that is possible for the improvement or correction of both.

From the standpoint of the male, it must be remembered that even a normally motile spermatozoan of normally mature morphology is not necessarily capable of fertilizing the egg, for the intangible factor of germ plasma quality still has to be reckoned with. It is in cases of this sort that thyroid therapy is often empirically used, and with not infrequent success. If there is one factor which more often than any other is apt to have been overlooked in patients who have previously had extensive investigation, it has in my experience been that of the thyroid status of the husband. Not infrequently a definite hypothyroidism is revealed, and thyroid therapy may turn the trick.—Ed.)

MISCELLANEOUS

ON CONSERVATION OF FUNCTION IN GYNECOLOGY

Victor Bonney

London, England

Radical extirpation of a uterus, ovary or tube which is functional or capable of having its function restored is an admission of surgical defeat against which the mind of every earnest surgeon naturally rebels; and the object of this paper is to show that the number of such defeats can be very substantially diminished.

Up to January 1945, the author had personally performed myomectomies 806 times. The fibroids were solitary in 40 per cent and multiple in 60 per cent of the cases, and the largest number of tumors removed from a single uterus was 225. There were 9 deaths in the series; an operative mortality of 1.1 per cent. The disturbed conditions which obtained in England during the war and which still continue, have prevented keeping in touch with the more recent cases, but in 1937 he published the results of a follow-up of 379 patients whose operations had been performed sufficiently long before to warrant a useful estimate of their remote results. New fibroids had appeared in 9 cases (2.3 per cent) and, making full allowance for the possibility of others having appeared since the investigation, it is certain that the recurrence rate is under 4 per cent. To achieve such a result it is absolutely necessary to remove every fibroid down to the smallest seedling. Menorrhagia, without recurrence of fibroids, either persisted or appeared subsequently 7 times.

Of the 137 patients who were married, within the childbearing age, and wishful to have children, 52 or 38 per cent conceived subsequent to their operations; and only one of these women miscarried, the rest being delivered of live children.

ADENOMYOMECTOMY

It occasionally happens that, the abdomen having been opened to perform myomectomy, the surgeon finds to his surprise, not a fibroid but an adenomyoma. What is he to do? Must he perforce remove the uterus? Not at all; the condition is an entirely innocent one, and the growth, unless very large, can be excised leaving the greater part of the uterus *in situ*. The author has performed the operation on and off during the last twenty years. All his patients recovered and, as far as he knows, there has been no recurrence in any one of them. This result proves that these growths are purely innocent and, incidentally, discloses the interesting fact that endometriosis of the uterine wall is a phase, not a habit of the endometrium.

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From the standpoint of the male, it must be remembered that even a normally motile spermatozoan of normally mature morphology is not necessarily capable of fertilizing the egg, for the intangible factor of germ plasma quality still has to be reckoned with. It is in cases of this sort that thyroid therapy is often empirically used, and with not infrequent success. If there is one factor which more often than any other is apt to have been over-looked in patients who have previously had extensive investigation, it has in my experience been that of the thyroid status of the husband. Not infrequently a definite hypothyroid-ism is revealed, and thyroid therapy may turn the trick.—Ed.)

deed, his recommendation of this in some conditions will impress many of us as unwisely ultraconservative. He is on very safe grounds in urging greater utilization of myomectomy rather than hysterectomy in the removal of fibroids in women in whom the possibility of future pregnancy is desired. Even very large and very numerous myomas can be removed without sacrificing the uterus, and the author has developed a special clamp, with rubber-covered blades, to compress the cervix and the uterine arteries and lessen the vascularity of the operation. The largest number of tumors which he has removed from a single uterus is 225, probably an all-time record.

When it comes to recommending, as he does, "excision" of adenomyosis of the uterus, his position is far more vulnerable. Adenomyosis is a diffuse lesion which involves considerable areas and often the whole uterine wall, and there is no way of determining its limits by inspection or palpation of the organ. I do not think that many will copy his conservative treatment of this condition.

As to the removal of benign cysts of the ovary (dermoid, follicular, endometrial and cystadenomatous) by enucleation rather than by oophorectomy, one must of course individualize. One will be far more conservative when the involved ovary is the only one possessed by the patient. Certainly follicular, often endometrial, and sometimes small dermoid cysts can be safely excised whether the patient has one or two ovaries. Bonney reports a case in which he enucleated 3 dermoids from each of the ovaries. With cystadenomas I believe that most of us would be much more cautious about "ovarian cystectomy," as Bonney calls this procedure of excision, and would much more frequently remove the involved ovary if the other is sound. This would apply especially to the serous papillary cystadenomas, and with many of these, as a matter of fact, the surgeon will under certain conditions feel justified in doing a complete operation even if the disease is unilateral.

Finally, the author appears less unenthusiastic than most of us about operations for the restoration of tubal patency, and reports results which are certainly far better than those commonly noted, with 18 per cent of successes. He never makes subsequent tests as to the patency or nonpatency of the tubes upon which he has operated, and his reason for this, as he says, is purely sentimental. Rather naively but not without wisdom, he says, "If reclosure is demonstrated it takes from the patient the happiness of hope and leaves her poor indeed. I trust the recording angel will drop a tear on this, my dereliction from scientific austerity."—Ed.)

THE GYNECOLOGIC ASPECT OF HEADACHES

Erwin O. Strassmann

The Department of Gynecology, Baylor University College of Medicine, Houston, Texas

Three undesirable companions follow women through life. Sometimes they appear single, sometimes combined. They are backache, constipation and headache. This unpleasant triad seems to be typical for the human female.

Backache is a penalty women pay for walking on their hind legs instead of on all four extremities. The primary arrangement of the genital organs provides for their leaning anteriorly toward the abdominal wall. The upright position,

OVARIAN CYSTECTOMY

Twenty years ago the author succeeded in enucleating a dermoid cyst from out of the ovary and, pursuing the implication, he was able eight years later to record a number of such operations, and announce that all innocent cysts (dermoid cysts, follicular cysts, chocolate cysts, and adenomatous cysts) were enucleatable, besides certain solid tumors such as fibromata and granulosa-cell tumors.

He has by now performed the operation over 300 times and it is a singularly safe procedure, every one of his patients having made a good recovery. He began by applying it to small cysts only, but, having gained confidence, he now employs it for large cysts as well, whenever the age and circumstances of the patient are best served by conservatism.

In 1937 he published the results of a follow-up of 90 of these cases and only in one of them had recurrence taken place, and even of this one he is not sure, as he was unable to obtain particulars of the operation. Of the 90 patients there were 40 who, being married and of childbearing age, desired children and of these 16 conceived after their operations. Five of the pregnancies occurred after the enucleation of chocolate cysts (bilateral in 2); six after the enucleation of serous cysts (bilateral in 2); four after the enucleation of dermoid cysts (bilateral in 2); and one after the enucleation of a solid granulosa tumor.

RESTORATION OF TUBAL PATENCY

For a number of years before the introduction of tubal insufflation the author had treated hydrosalpinx by making a new stoma, ignorant of the fact that the essence of hydrosalpinx is that both ends of the tubes are closed. Naturally, as regards subsequent pregnancy he had no successes, and he expects other surgeons had the same experience. Rubin's discovery altered all that and the author designed an intrauterine nozzle, like a Hegar's dilator, with a disc on it two and a half inches from its upper end, so that the nozzle could be kept fixed in the uterus by the pressure of gauze packed into the vagina against the disc. By this device the effect of blowing air or gas into the uterus can be watched through the abdominal incision; while if air is blown down the tube from its outer end, and any of it reaches the uterine cavity, the needle of the manometer will rise.

In 1937 the author sent a *questionnaire* to 55 patients whose tubes he had reopened and received 37 replies. Seven of them had conceived as follows: after external salpingostomy, 2 cases; after reimplantation, 2 cases; after external salpingostomy on 1 side and reimplantation on the other, 1 case; after double reimplantation and double salpingostomy, 1 case; and after partial tubal exsection and anastomosis on both sides, 1 case. His proportion of successes, therefore, was 18 per cent; not a figure to boast about, he states, though somewhat better than many which have been published.

(It is of interest that the staunchest champion of radical surgery for cervical cancer, throughout the long years in which radiotherapy was almost universally the popular plan, should also be a strong advocate of conservative surgery for various benign lesions. In-

can only be accepted as present after all physical causes have been eliminated and after the background, surroundings, constitution and character have been carefully investigated.

(While the author's division of typical women's headaches into the neurogenic, hormogenic and psychogenic is not illogical, it must be remembered that women are also subject to headaches due to many other possible causes, just as are men. Nor is it always easy to put one's finger on even a reasonably presumptive cause.

The illustration which the author selects for the neurogenic group is one which will not seem impressive to many, although I suppose its possibility cannot be denied. I do not know whether many headaches can be cured by treating the uterosacral ligaments or a chronic parametritis. This would seem not unlike the treatment of dysmenorrhea by cocainizing the genital areas in the nose, a method of therapy highly popular in the preceding generation. According to many excellent gynecologists of that day, it was highly successful, though we now look back on this so-called Fliess treatment as representing only a form of psychotherapy. Perhaps a better illustration of the neurogenic type of headache would be that due to nerve exhaustion, seen in high-strung women who burn up a lot of nerve energy, paying the penalty with headaches as well as other nervous symptoms.

Another category difficult to outline clearly is the hormonogenic, which one would think of chiefly in the headaches sharply limited to about the time of menstruation, and not occurring at any other time. This is the type often spoken of as pituitary in origin, though this explanation is just as unprovable as that suggested by Strassman, that they are due to periodic lack of estrogenic hormone. It seems unwarranted to extend this hypothesis to genuine migraine, which occurs in men as well as in women, and which, in my experience, is rarely limited to the period of menstrual bleeding, although there may be a predilection for this phase.

As for the psychogenic group, the author is on safe ground in recognizing this as a frequent and important group, but there appears to be no necessity for linking this up, as he does, with the "low tide of estrogens" in the premenstrual phase and in the menopause. —Ed.)

THE PELVIC FASCIA: ITS SIGNIFICANCE TO THE SURGEON

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The two main divisions of the pelvic fascia listed in the Basel Nomina Anatomica are: (A) the superior fascia of the pelvic diaphragm; (B) the endopelvic fascia.

The superior fascia of the pelvic diaphragm is a continuation of the aponeurotic lining of the abdominal cavity. It has three components: (1) the aponeurosis of the ileo-coccygeal portion of the levator ani which covers the obturator muscle; (2) the ischio-coccygeus muscle or its fibrous vestige; (3) the aponeurosis of the pubo-coccygeal portion of the levator ani.

The portions of the superior fascia of the pelvic diaphragm which are impor-

standing as well as sitting, changes the direction of the abdominal pressure. Any additional force or weakness of the supporting ligaments can result in retrodisplacement of the entire tract, mainly the uterus, with subsequent swelling and descent. Backache is the result.

Constipation is the penalty women pay for irregular eating, elimination habits and especially for insufficient physical activities. It is their widely emphasized but wrong conception that domestic activities inside the house are as good as physical exercises outdoors.

Headache finally is the penalty women pay for the privilege of preparing for conception each month. It is this monthly up and down cycle, the preparation for pregnancy and the events following the elimination of the unfertilized ovum, which disrupts the stability of almost every system in the female and leads among other symptoms to the very outstanding one, headache.

There are three types of headache which are typical for women, the neurogenic, the hormonogenic and the psychogenic. In making this division, it should be clearly understood that all three of them are closely knit together in their action as well as in their results. It is, however, necessary to include a more or less artificial grouping according to the prevailing mechanism.

As an example of the neurogenic type of headache the author mentions the occipital "pain in the neck" which is so often found in combination with backache. In this instance the seat of the ailment is the uterosacral ligaments. Here there occurs a thickening of the posterior parametrium, the tissues which contain the peripheral nerves and the Frankenhaeuser ganglion. These structures run from the isthmus of the uterus upwards and posteriorly, hugging the rectum on either side to the sacrum. They are the main support of the uterus. Any pressure from above will put these ligaments under strain. Any chronic infection of the cervix may lead to swelling, thickening and final shrinking of the uterosacral ligaments. The pain associated with this posterior parametritis is primarily felt as backache. But for some unknown reason, it secondarily leads frequently to headache, which is located in the back of the head and toward the neck. The preferable method of treatment is conservative, and consists of internal and external application of wet and dry heat, dehydrating tampons, cauterization conization of the cervix and rest periods during the day.

The *hormonogenic* type of headache begins with the menarche, follows the patient through some thirty years of menstrual life and disappears after the menopause. It is strictly connected with the low tide of ovarian hormones and appears therefore most frequently just before or during the first few days of menstruation. The most effective remedy for this type of headache is estrogenic hormones as prophylaxis, and ergotamine tartrate as a therapeutic measure. The corpus luteum hormone has also proved to be of value in the premenstrual phase.

The third and final type of headache in women is the *psychogenic* type. It is closely connected with the hormonogenic since the low tide of estrogens in the premenstrual phase and in the menopause predisposes to psychic lability and complex mental reactions. Psychogenic headache like other psychogenic ailments

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tant are: (1) the lateral pubo-vesical ligament. It is the true lateral ligament of the bladder and runs from the pubic ramus to the base of the bladder and cervix. (2) The middle pubo-vesical ligament. This is the true anterior ligament of the bladder and is the rounded edge of the pubo-coccygeal aponeurosis stretching between the pubis and the bladder.

The endopelvic fascia is the fibro-fatty mass which arises near the pelvic inlet and passes medially to incorporate the pelvic viscera, vessels and nerves.

The special condensations of this endopelvic fascia are: (1) the tendinous arch of the pelvic fascia. This extends principally from the pubis to the ischial spine. (2) The neurovascular sheath. It is also called the cardinal ligament and starts as a thick fibro-fatty mass covering the sacrosciatic foramen and pyriformis muscle. It passes medially as a sheath for the viscera, vessels and nerves. It grows more condensed and enriched with involuntary muscle fibers as it passes medially to become continuous with the cervix and lateral vaginal walls. (3) The utero-sacral ligament. This is the lower part of the neuro-vascular sheath slinging the bladder and the uterus to the sacrum. (4) The Allantoic sheath. This has been named the false lateral ligament of the bladder. It is a lamina raised from the common neurovascular sheath by the umbilical artery in its ascent from the hypogastric. A knowledge of the dimensions of the allantoic sheath is important in understanding the limits and direction of spread of extravasation. (5) The umbilico-prevesical fascia. This is a lamina which runs in triangular shape from the neck of the bladder to the umbilicus. (6) The broad ligament. Superiorly this is composed of a thin lamina stretching between the allantoic sheath and uterus; but is dense at its base where the neurovascular sheath is encountered as the parametrium. (7) The sheath of the rectum. (8) The presacral fascia. This structure is of importance in doing a presacral neurectomy. When it is picked up in front of the sacral promontory its densest part is encountered, and by wide and free dissection here one is certain of removing the whole plexus.

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ERRATUM

In the editorial note on page 25 of the February, 1948 issue, the clause in the eighth and ninth lines "and on retrospect we have found reason to regret this policy" should read "and on retrospect we have found *no* reason to regret this policy."

Obstetrics

PHYSIOLOGY OF PREGNANCY, LABOR AND PUERPERIUM

THE PROBLEM OF FERTILIZATION

Lord Rothschild

Given at London Jewish Hospital Medical Society

Fertilization may be defined as the incitement of the egg to development by a spermatozoon and the conveyance of paternal qualities to the egg. Its central problem is: What does the spermatozoon do to the egg which transforms it from being an inert and somewhat moribund cell into a highly organized and differentiated embryo?

The egg is usually fairly large (in humans about the size of a small pin's head), often due to the presence of nutrient material. The spermatozoon is usually extremely small. It consists of a head of nuclear material, a middle piece, the functions of which are not clearly understood, and a vibratile tail. The relative sizes of the human egg and spermatozoon head are about those of a football and a marble.

"The main characteristics of the fertilization reaction are: (1) Both eggs and spermatozoa must be ripe for fertilization to take place. (2) Fertilization is specific; that is to say, crosses between different species or genera can rarely be achieved, or, if they are, the chances of a normal embryo resulting are small. (3) Fertilization is an irreversible phenomenon in nature. (4) Only one spermatozoon fertilizes an egg. (5) After adhesion of the spermatozoon to the egg surface a membrane, the fertilization membrane, is thrown off from this surface. (6) The head of the spermatozoon rotates through 180 degrees when it has passed through the egg surface. (7) The head of the spermatozoon within the egg and the nucleus of the egg travel through the cell on somewhat curved and different paths to meet in about the center of the egg. Then fertilization merges into cell division and development." These are the significant characteristics, although there are additions and exceptions.

The first part of the fertilization, activation, which occurs immediately after the spermatozoon has adhered to the egg surface, involves the prevention of other spermatozoa from getting in, the elevation of the fertilization membrane, and the irreversibility of the reaction.

There has long been a tendency to consider the unfertilized egg as being in an inhibited condition which is rectified by fertilization. After fertilization one might expect alterations in the egg surface which would permit a greater degree of interaction between the egg and its environment. R. S. Lillie found with sparingly ionized substances a temporary increase in the permeability of sea-

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surfaces of the spermatozoa sufficiently similar to that between an egg and a spermatozoon to alter the spermatozoon in an irreversible manner. The idea of the spermatozoon "muzzled" in this way explains the microscopic observation that spermatozoa can bump against the surface of an egg and then swim away without adhering, and provides a further reason for the vast number of spermatozoa needed. There may be significance in the chemical similarity between vitamin K_1 and echinochrome, which Kuhn and Wallenfels consider to be the agent in fertilizin responsible for increasing spermatozoan activity.

The conditions of the egg as unfertilized, being fertilized, fertilized, and dead, should be reflected in the biochemistry and particularly the metabolism of the cell. Mere measurement of oxygen consumption is inadequate. The current facts and speculations about metabolism during the early phases of the fertilization reaction suggest that activation may be associated both with anaerobic processes (in which case the acid which diffuses out of the egg might be a product of anaerobic glycolysis) and with aerobic ones involving the breakdown of fats and proteins. Research on the question of metabolic difference between unfertilized and actually fertilized eggs has led to a theory that fertilization induces a cytochrome type of metabolism, while the unfertilized egg respires through a non-ferrous autoxidizable carrier of the flavin or pyocyanine type, the cytochrome being present but inactivated. The results here have been disputed, however, and repetition of the experiments is needed.

(It is to be hoped that continued studies on seminal fluid, such as Lord Rothschild touches upon, will sooner or later provide information of practical value in the management of male sterility. To date, however, the results have not been impressive. For example, the addition of hyaluronidase to human semen of low sperm count does not appear to increase its fertilizing potency; and as far as I am aware, only negative results have been reported from other attempts to use this enzyme in the treatment of sterility.

In regard to immunizing animals or persons against hyaluronidase, sperm or any other component of semen and thereby causing temporary sterility, this idea has intrigued investigators for many years and several workers claim to have produced sterility in this manner both in experimental animals and in women. However, in a study carried out on female rats by Guttmacher, Stewart and myself (Jour. Contraception *4:* 147, 1939), neither the repeated injection of whole semen or spermatozoa (rat, ram, dog, horse) caused any significant reduction in fertility. We are hence skeptical.—Ed.)

urchin eggs after fertilization—not in total capacity but in rate of osmosis. It does not follow that there will be relatively large changes in the electrical properties of the surface or in the electrical capacity. There is an increase in the electrical capacity of the sea-urchin plasma membrane, but it may be caused by the thinning of the membrane. During the fertilization reaction an unidentified but fairly strong acid diffuses out of the sea-urchin egg; measurement of possible electrical changes here has so far met great technical difficulties. The investigation of other eggs in regard to acid production is urgently required.

The change which prevents other spermatozoa from getting in must be propagated relatively rapidly from the point of attachment of the fertilizing spermatozoon—probably no slower than 1 mm. per second, and probably completed long before the elevation of the fertilization membrane.

The great number of spermatozoa—about 400,000,000 in a human ejaculation for the fertilization of 1 or perhaps 2 eggs—has been thought necessary for a very high probability of fertilization. However, research shows other factors. Freshly ovulated mammalian eggs are surrounded by follicle cells, which obviously make it difficult for the spermatozoa to come into contact with the egg. Mammalian testes and spermatozoa contain an enzyme, hyaluronidase, which disperses these follicle cells, or dissolves the substances which make them stick to the egg. The hyaluronidase of the first lot of spermatozoa to reach the egg disperses the follicle cells, leaving the egg bare for fertilization. So large a number is necessary for an adequate concentration of the enzyme, since hyaluronidase in human semen is proportional to the number of spermatozoa present.

Female rats can be immunized against bull testes' hyaluronidase and the immune serum prevents the eggs being denuded of their follicle cells in vitro. Furthermore, normal rat semen itself contains appreciable amounts of an inhibiting substance. Two implications follow. First, it may be that new methods of contraception may be developed by the use of immunized blood sera; secondly, certain cases of sterility may be due to the inhibiting effect of blood on the enzyme's activity. Certain types of sterility previously attributed to a hypothetical spermatozoon immunity may be due to antibodies, formed against hyaluronidase, passing from the serum into the uterine fluid.

In lower organisms the implications are not clear, though there are still enormous numbers of spermatozoa, and an enzyme may be needed for them to pass through the protein coverings around many eggs.

A complicated phenomenon is the appearance of a substance called fertilizin in the medium around unfertilized eggs, at least in marine invertebrates (first demonstrated by F. R. Lillie). Suspensions of spermatozoa maintain a higher rate of metabolic and mechanical activity in the presence of fertilizin, which may increase the probability of any particular spermatozoon reaching and fertilizing the egg, though fertilizin is not essential for fertilization. An agglutination of sperm, which cannot be disrupted by shaking but which disintegrates spontaneously, also takes place in the presence of fertilizin. After agglutinating spermatozoa markedly lose their capacity to fertilize eggs, even though their activity is not impaired (Tyler, 1941)—as though there may be some reaction between the

rior pituitary preparations should be used with caution in all serious cases of heart disease, especially in the presence of congenital intracardiac shunts. Since uterine contractions may result in repeated small autotransfusions, producing transient rises in venous pressure and filtration of fluid from the capillaries, thus gradually diminishing total blood volume during labor, normal labor may be tolerated better than abrupt delivery.

Unusual technical difficulties were encountered in attempting to measure plasma volume with the dye T-1824, both before and after delivery. The possibility of large pools of blood in pelvis, legs, or other reservoirs is suggested. The results of hematocrit determinations and of these estimations of blood volume which appeared to be technically satisfactory agreed with other evidence indicating that (a) at about the time of delivery a significant volume of fluid leaves the vascular compartment; (b) on the second or subsequent days of the puerperium a volume even greater returns to the blood stream; and (c) the final return to normal nonpregnant blood volume probably occurs after this as a result of the postpartum diuresis.

Though the total evidence is inconclusive, the close analogy between the changes in blood volume, hematocrit, and venous pressure at delivery and changes known to follow obliteration of large arteriovenous fistulas suggest that the uterus at term contains a shunt of important proportions. The repeated uterine contractions, by temporary occlusion of the placental circulation, may prepare the cardiovascular system for permanent occlusion of the shunt. 4 tables, 4 charts, 2 figures.

(This paper is of especial importance from 2 points of view. In the first place, it properly stresses the early puerperium as a critical period for patients with advanced heart disease. The other critical time, of course, is around the 28th week of pregnancy when the load imposed on the heart by the rising minute output reaches its height. The hazards of the first few postpartal days, however, are particularly deserving of stress because they are not widely appreciated. As a result, treatment may be neglected (oxygen therapy, etc.), and more specifically, the grievous error may be made of carrying out tubal ligation at this time. I know of 2 Baltimore deaths from this cause in Class III cardiacs who had apparently come through labor without evidence of cardiac difficulty.

The second important point made by the authors is that the cause for the tendency to heart failure during the first few days of the puerperium, is an increased blood volume. This is a natural and inevitable transition state in the course of transfer of fluids from the tissues to the urine just before the well-known diuresis of the 3rd to 5th day takes place. Among the many studies on blood volume in pregnancy, not one, so far as I can recall, has reported day to day changes in the early puerperium and it is hence gratifying to see that a few observations are beginning to be made on circulatory changes during this important "reconversion" period.—Ed.)

PHYSIOLOGIC CHANGES IN THE CIRCULATION DURING AND AFTER OBSTETRIC LABOR

Ellen Brown, John J. Sampson, Edwin O. Wheeler, Benjamin F. Gundelfinger, and Joseph E. Giansiracusa

San Francisco

In terms of fatality and congestive failure, the early puerperium is apparently the most critical period for patients with serious heart disease. In relation to postpartum circulatory failure, 2 questions arise: (a) how important is the load imposed on the heart by the work of labor, and (b) what are the effects on the circulation of emptying the uterus, whether by cesarean section or by active labor?

Oxygen consumption studies have shown that the work of labor is variable but often severe, and the "oxygen debt" incurred during a long and hard second stage may not be repaid for over an hour after delivery. Changes in pulse and respiratory rate reflect the same situation. Statistical evidence however indicates that emptying the uterus may itself place a burden on the heart. In patients with serious heart disease, deaths from congestive failure occur with equal or greater frequency following cesarean section, where the work of labor is excluded, than following vaginal delivery.

In the present study, repeated determinations of heart rate, blood pressure, venous pressure, vital capacity, circulation time, plasma volume, and venous hematocrit were made during and after labor in 13 normal and 3 cardiac patients with uncomplicated vaginal deliveries and 2 normal patients delivered by cesarean section. Two normal patients and 1 with heart disease delivered vaginally and 3 normal patients delivered by cesarean section were studied in regard to the first 4 factors. Observations of pulse rate, blood pressure and venous pressure were made on 9 patients, delivered uneventfully, from whom oxytocic drugs were withheld until their need was evident. It was attempted to determine whether the load imposed on the heart by delivery is primarily the result of (a) the work of labor, (b) more or less sudden obliteration of a vascular shunt in the uterus, or (c) a combination of these and possibly other factors.

The changes in heart rate, arterial blood pressure, vital capacity and circulation time were not sufficiently uniform to point to definite conclusions.

Venous pressure increased significantly and often to abnormal levels during the first 24 hours after delivery in all patients who received routine medications. Further evidence, including administration of ergotrate to nonpuerperal hospital patients, indicated that the rise in venous pressure could be attributed to the effects of ergotrate. To the reduction in capacity of the vascular tree generally attributed to the oxytocics may be added increased return of blood to the heart from exercising muscles, autotransfusion of blood expressed from the uterus by the action of oxytocic agents, and a possible increase in overall resistance coincident with occlusion of a vascular shunt. Ergot derivatives and probably poste-

8. Her perineum was irrigated with ½% lysol every 6 hours until discharged. The patient was taught as soon as possible to do this herself and each patient had her own individual dish with dressings.

9. If the patient had an episiotomy, light was applied twice a day for 30 minutes and sutured areas were painted with metaphen. If the sutures did not look well and showed any sign of suppuration, sulfathiazole was powdered about them.

10. The patient was allowed to go the the bathroom if there was one in her room, on the second P.P. day, but was accompanied by a nurse. Ambulation must be gradual, and by the fifth day the patient is pretty well up at will. She was encouraged to pass her own water, but if necessary, was catheterized. This was followed by irrigation with boracic solution.

11. If her Hbg. was under 70%, ferrous sulphate gr. 5 were prescribed 3 times a day.

12. A light diet was prescribed as soon as the patient tolerated it, and full diet was given after the first movement, which was usually about the third day.

13. Fluids were pushed, the patient was encouraged to take 8 to 10 glasses of water, fruit juices, or milk daily.

14. The patient was encouraged to lie on her stomach on the second day, starting at 10 minutes, then twice daily and gradually increasing.

15. On the fourth day she was shown how to do the knee-chest position or whatever exercises were instituted and she started at these on the fourth day.

16. If the patient had had sutures, no attempt was made to have her take exercises, such as the knee-chest position, until after the sixth P.P. day.

17. For the repair of episiotomy No. 0 chromic catgut was used throughout, excepting in the skin which was closed by interrupted sutures of dermol. The dermol was removed on the 7th or 8th day, according to when the patient was to leave hospital and how well the skin was healed.

On the average, the first day out of bed among the early ambulatory patients was the second day postpartum (largely because of the lack of nurses some patients did not get out of bed until the third day); among the late risers, the ninth postpartum day. All patients in the former group went home by car or taxi after an average stay of 9 days, while the others went home, 8 in ambulances, after an average stay of nearly 11 days. There was some difference in catheterization rate, and striking result in the bowel movements, where 102 of the early risers had a bowel movement before the fourth postpartum day, and only 43 late risers had. In the early ambulatory patients involution seemed better, flow of milk seemed to be stimulated, and there was no predisposition to prolapse and retroversion.

Early rising results in more rapid and *comfortable* convalescence, with less asthenia and less depression, less medication and rectal treatment required, simplified and decreased nursing care, and far more rapid return to normal body function. Patients approve, and the improvement in morale is tremendous. There is no delay in the healing of the perineum. The incidence of retroversions, postoperative invalidism, and complications is reduced, and home convalescence is speeded.

MANAGEMENT OF NORMAL PREGNANCY, LABOR AND PUERPERIUM

EARLY AMBULATION IN THE PRACTICE OF OBSTETRICS

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Toronto, Ontario

Although there are earlier reports on early ambulation in obstetrics and in surgery, and Greenhill believes 90 per cent of his patients could be permitted out of bed on the first day, physicians generally have frowned on the idea of permitting a woman to get out of bed too soon after delivery, because of fear that the episiotomy would break down, that there might be too much strain on the pelvic floor, resulting in prolapse and retroversion, or that postpartum hemorrhage might occur.

Recently, however, as in wartime obstetric reports from London and in the work of Daniel Leithauser of Detroit with surgical patients, evidence has been collected to prove that early rising is beneficial to the patient.

For study, the author took at random 250 women he had delivered, 125 before May, 1944, who did not participate in early rising, and 125 delivered after May, 1944, after he instituted early rising. The postpartum care for the 2 groups did not vary essentially, except that in the early ambulatory patients an enema was substituted for castor oil and a routine which led to their being up walking about by the fifth postpartum day was used on all uncomplicated parturients; breech extraction, twins, use of forceps, and episiotomy were not considered contraindications.

The procedure was as follows:

1. Ergot tartrate, tablet 1, was given every 4 hours, after delivery, for 24 hours.
2. A.P.C.&C. (2) were given for after-pains, and repeated every 2 or 3 hours if necessary.
3. Mineral oil, oz. 1, given night and morning starting on the second P.P. day, for 2 days.
4. An S.S. enema was given on the 4th day if the patient had no bowel movement.
5. The patient was allowed to stand, encouraged to cough on the 1st P.P. day (if the patient was delivered before 4 a.m., it would be considered her 1st P.P. day, and if she were delivered after 4 a.m., she did not get up until the 2nd P.P. day). The patient was allowed and encouraged to move about on the bed, encouraged to lie on her stomach and was offered a light diet.
6. On the second P.P. day, she sat in the chair for 5 minutes.
7. On the third day the patient was allowed up to sit in a chair and encouraged to walk.

clude toxemias of pregnancy, intrauterine fetal death, premature rupture of the membranes, post-maturity and marked hydramnios. Cephalopelvic dispropor- tion is a contraindication.

· Among 25 cases, none prior to 36 weeks, the method was successful in 20—that is, labor pains began within 6 hours of the last dose of Partergine. In many, doses were continued even until the patient was having pains every 7–10 minutes in order to increase the strength and frequency of contractions.

· The cervix was not taken up in 5 of the 9 primigravidae, and partly in 4. Of the 11 multiparae, the cervix was not taken up in 3, partly taken up in 7, and com- pletely in 1 case. Among the failures the cervix was not taken up in 3 and par- tially in 2.

There was no appreciable change in the mother's blood pressure, pulse, or res- piration, no gastrointestinal upset, no change in the postpartum period in terms of either duration or blood loss.

The effect of Partergine appeared first as a complaint of backache and lower abdominal discomfort, more or less simultaneous, followed shortly by definite uterine contractions. There was no tetany, although in one case the uterus be- tween contractions remained more tense than usual for a time. Length of labor appeared slightly shorter than normal.

· No untoward effect on the fetus appeared in the whole group. Excluding a hydrocephalus which was perforated, one stillbirth followed a very difficult for- ceps delivery for arrest at the outlet in the occipito-posterior position. Post- mortem examination revealed massive intracranial hemorrhage. Partergine seemed to cause no disturbance in rate or volume of the heart, either in this or the other fetuses.

Partergine appears as successful in induction of labor as any of the better known methods, and much safer than Ergometrine. Oral administration causes less physical disturbance to the patient. Farber of Philadelphia has found similar results with Methergine.

· As with all oxytocics, precautions must be taken. Magnesium ion (intrave- nously, 2 cc. of 50 per cent solution of magnesium sulfate or 10 cc. of 20 per cent solution of magnesium gluconate) is suggested as a possible antidote for uterine tetany.

Three increasing factors, analgesia, anesthesia and operative delivery, tend to interfere with the normal third stage of labor. Placental separation seems to de- pend on the contractility of the uterus, the sudden reduction of the surface area of the placental site, and the more rapidly the reduction takes place, the more complete will be the separation and the less the blood loss. Intramuscular Ergo- metrine and posterior pituitary extract have been used, but their relatively slow action probably only expels the already separated placenta. Intravenous Ergo- metrine brings sudden uterine contraction of maximum intensity and tone.

After the birth of the anterior shoulder, 0.125 mgm. Ergometrine is given intra- venously. During the 20–30 seconds before it acts on the uterus, delivery can be safely completed. (No attempt has been made to use the technique in breech

Contraindications are prolonged preoperative bed rest (as in cardiac insuffi-ciency), serious anemia and shock, retained placenta, hemorrhage, thrombi, long and difficult deliveries, and suspected infection.

If such a program is to be undertaken, it must be carried out in detail. The patient must be up walking, not sitting. The best time is 24–36 hours postpar-tum. Many postoperative complications are apparent in a patient during the first 24 to 36 hours. Later than 3 or 4 days, few benefits are obtained, and it is better to keep the patient in bed. 2 tables.

(Early puerperal rising is becoming almost routine in the United States and most of us, I am sure, would agree with Bryant as to its salutary effects. There are still skeptics, however, and for these the beneficial results which Bryant reports in his early risers, when compared with his late risers, should prove informative.

The author, it will be noted, devotes a great deal of attention to the episiotomy wound, irrigating it with ½ per cent lysol every 6 hours, applying light twice a day and painting the sutured areas with metaphen. Moreover, "if the sutures did not look well and showed any sign of suppuration, sulfathiazole was powdered about them." I may be mistaken, but all this makes me suspect that the author uses mediolateral episiotomy. Those of us who employ routine median episiotomy find it much easier to repair; we save a huge amount in electricity for light treatments; we economize on time because we do not have to listen to complaints about the stitches; and at the 6 weeks return visit, a virginal introitus presents itself. It seems to me that someone should start a campaign in behalf of routine median episiotomy. I know quite a number of women who have had both types and would gladly contribute testimonials.—Ed.)

THE USE OF ERGOT FOR INDUCTION OF LABOR AND FOR THE THIRD STAGE OF LABOR

W. D. A. Callam

Powdered ergot, the growths in diseased rye, has been used for at least 4 cen-turies to hasten labor. Three principal alkaloids from ergot are now used—Ergotoxine, Ergotamine, and Ergometrine (also known as Ergonovine, Ergotocin, Ergosterine, and Ergobasine). Partergine, a substance recently produced semi-synthetically by Sandoz, through alteration of the Erbobasine molecule, is used in this series of cases. Prepared for oral administration, 0.075 mgm. methyl-ergobasine tartrate per cc. of solution, it is similar to Methergine in America, and has about twice the effect of Ergobasine.

At 5 a.m. the patient is given 1 ounce of castor oil, 1 hour later a warm soap and water enema. At 11 a.m. 1/2 cc. of Partergine diluted in 10–15 cc. of water is given orally, preferably on an empty stomach for quicker absorption, repeated if required for 3 half-hourly doses. Great caution is necessary. If labor is not established, the Partergine is repeated on the 2 following days. Indications in-

PATHOLOGY OF PREGNANCY

OLIGURIA AFTER ABORTION

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Clin. Sc. 6: 173–186, 1947

The meager publications on renal failure complicating abortion have recently been reviewed by O'Sullivan and Spitzer (J. Obst. & Gynaec. Brit. Emp., 53: 158, 1946) and so far only 19 cases have been reported.   The history, routine investigations and clinical picture excluded as far as possible the known causes of oliguria after abortion other than a syndrome attributed to septic abortion and symmetrical cortical necrosis of the kidneys.   The "known causes" excluded were: incompatible blood transfusions, acute nephritis, pyelonephritis, renal damage due to sulfonamides, hemoglobinuria from sensitivity to quinine and toxic nephritis due to ingested poisons.

In symmetrical cortical necrosis of the kidney, the kidneys show tubular changes with cellular necrosis, interstitial edema and polymorphonuclear leucocytic infiltration.   They appear to correspond closely with the kidneys of soldiers dying with oliguria after severe trauma associated with sepsis and often with injury to a main blood vessel.   Duff and More in 1941 reviewed 71 proved cases of cortical necrosis, 48 associated with pregnancy and 23 with severe infections (Am. J. Med. Sci., 201: 428, 1941).   The condition may occur with abortion, although it is more common toward the end of pregnancy when it may follow abruptio placentae with concealed hemorrhage.   The clinical picture is one of profound oliguria or anuria following abortion or premature labor, with death usually occurring between the 4th and 12th day.   The patients become increasingly edematous; mental clarity is retained but the blood urea rises to high levels. The very scanty urine may be blood stained at first.

The present paper describes the clinical features and biochemical findings in 4 cases of acute renal failure after abortion.   They were admitted over a period of 20 months to a Department dealing with approximately 400 abortions annually. All 4 patients had oliguria persisting for 6, 10, 13, and 14 days after admission. During this time their blood urea rose to 365, 550, 400 and 304 mg. per 100 cc. respectively.   They were extremely ill, with troublesome vomiting, but remained clear mentally.   They were treated conservatively and after a spontaneous diuresis recovered completely.

The chief interest of the biochemical findings lay in the severe loss of renal function which they showed and the large and abrupt departure from normal electrolyte concentration which the body will tolerate without gross evidence of further tissue damage, or of mental changes, other than a peculiar listless anxiety.   In Case 1, the urine for 14 days was an almost unadulterated glomerular filtrate, and

deliveries.) With the sudden uterine contraction, the placenta is separated and pushed into the lower segment or vagina, and should be expressed manually with the aid of slight traction on the cord if necessary.

In none of the 100 cases studied was there excessive hemorrhage. Blood loss was estimated as minimal (under 100–150 cc.) in 75 per cent. The length of the third state was shortened; in only 3 per cent was it over 20 minutes. One manual removal was required. Davis and Boynton (1942) and others have found similar results with this method, preferable to use of Ergometrine following delivery of the placenta. There seemed to be no delayed postpartum hemorrhage.

Comment on the paper was chiefly concerned with the usefulness of ergometrine in the management of the third stage. 3 tables.

(This is at least the 3rd report which has appeared in the last 2 years recommending the use of methergine, a synthetic ergot preparation, for the induction of labor. The other 2 were contributed by American obstetricians, one by E. P. Farber of Philadelphia (Am. J. Obst. & Gynec., *51:* 859, 1946) and the other by J. C. Brougher (West. J. Surg., *55:* 371, 1947). Both these papers were abstracted in the Survey (*1:* 618, 1946 and *2:* 762, 1947) and in editorial notes appended it was observed that great caution must be exercised in using any ergot preparation for inducing labor. Certainly, the record of ergonovine for this purpose is very bad, since several cases of severe tetanic contraction with fetal death are on record. Farber, however, emphasizes the fact that methergine differs decidedly in its action from ergonovine, while in the above paper Callam observes that it is "much safer than Ergometrine" (ergonovine).

The 3 papers report a total of 75 inductions with methergine without the slightest evidence of deleterious effect on mother or infant; and if the 13 later cases recorded by Farber in a footnote are added, the total reaches 88. This is very reassuring in regard to the safety of the drug; nevertheless, in view of the danger of ergonovine when given antepartum, the burden of proof is on the methergine proponents and a still larger series would seem necessary before its complete safety can be established. As for its efficacy, the study of Brougher is not especially convincing. He compared the effects of methergine and pitocin for the induction of labor, 20 cases each, but ruptured the membranes (let it be noted) after the 3rd or 4th injection of each agent. The latent period before the onset of labor was 5.03 hours with methergine and 3.1 hours with pitocin. The length of the labors induced with methergine averaged 10.2 hours, with pitocin 8.3 hours. In other words, pitocin, in this small series, showed up better.—Ed.)

lowed rapidly by a breakdown in kidney function with oliguria, azotemia and death. At autopsy both the primary uteroplacental lesion and the renal lesion resembled those of abruptio. Moreover, the latter presented the classical picture of a "transfusion" or "crushing injury" kidney, as described above.—Ed.)

PREVENTION OF REPEATED MISCARRIAGE

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Am. J. Surg., 74: 143–149, 1947

The authors discuss various causative factors in the production of repeated miscarriage and point out that the treatment and prevention of repeated miscarriage are still in the experimental stage. They state that any patient who has had 2 miscarriages, and/or who shows clear evidence of endocrine genital dysfunction or hypoplasia with occurrence of even one miscarriage, should be investigated as to glandular and genital capabilities.

In this paper, the writers report a series of 27 patients who had miscarried from one to 3 times previously. Treatment was begun as soon as a diagnosis of pregnancy was established or suspected, and consisted of the following:

Anterior pituitary-like hormone, 1,000 to 2,000 units 3 times a week until 4½ months' gestation, then 1,000 units 2 times a week until 8 months.

Corpus luteum hormone, 5 mg. 3 times a week until 4½ months' gestation, then twice a week until 8 months.

Estrogen—alpha-estradiol, ½ to 1 mg. daily, depending upon the extent of uterine and genital hypoplasia present.

As a result of treatment, 27 babies were delivered, all of which were normal except one, which was a Mongol. There were no postpartum hemorrhages and no unusual complications during labor or the puerperium. Types of delivery were unaffected. Cesarean section was performed in 4 cases.

Labor did not set in earlier than 10 days after discontinuance of therapy. In most cases a lapse of approximately 3 weeks occurred. In several other cases in which corpus luteum hormone had been given without anterior pituitary-like hormone, bleeding occurred about 3 weeks after stopping of therapy, at 4, 4½ and 6 months, respectively.

The authors are inclined to give their more recent patients larger doses of anterior pituitary-like hormone in the early months, namely, 2,000 units 3 times a week, and trust that this will tend to prevent the bleeding which occurred in the first trimester in some cases.

Therapy for repeated miscarriage should be prophylactic. Treatment begun after miscarriage has already threatened is in many instances hopeless, as the fetus is often beyond help or entirely resorbed; however, such treatment should be instituted until a definite diagnosis can be made, as some cases will be carried through successfully.

in Cases 2 and 3 there was evidence of only 2 to 4 fold concentration by re-absorption of water, for periods of 12 days and 10 days, respectively. The plasma chloride levels fell very low.

Although 3 patients showed a rise in serum potassium to levels of 20.5, 27.5 and 42.5 mg. per 100 cc., only in Case 3 was the rise sufficient to cause alarm. Potassium liberated by endogenous cellular breakdown was in part diluted by retained water, but the patient in Case 3 (alone of the 4) was given drinks flavored with synthetic flavorings instead of plain lactose and saline. Analysis of these fruit drinks, diluted as for use, revealed a potassium content of 8–11 mg. K per 100 cc. Their use was stopped immediately but not before a remarkable electrocardiographic picture had been obtained when the serum potassium was 40.0 and the calcium concentration 6.0 mg. per 100 cc. (absent P. waves and extremely large T waves). Serum sodium levels varied less than those of the other electrolytes but tended to be high. As inorganic phosphorus values rose, those for calcium fell, reaching the low level of 5.8 mg. per 100 cc. in the one case in which calcium was studied. Despite low calcium values no tetany was seen.

Plasma values for inorganic sulfur rose in Case 3 between the 3rd and 15th days from 10 to 35 mg. per 100 cc. This was attributed to endogenous protein breakdown, calculated on this basis to be 57 gr. per diem.

From the biochemical data it is obvious that glomerular and tubular functions were equally, and almost wholly, suppressed. The whole picture is consistent with a temporary but great reduction in flow of blood through the afferent arterioles, so that the intraglomerular pressure was too low to permit glomerular filtration, but sufficient oxygen was available to prevent autolysis of the tubular and glomerular cells. The reduction seems to be most readily explained by spasm with or without thrombosis of the afferent small arteries and arterioles. The underlying pathological process is uncertain, but the most probable is that whose end-result is found in persons dying with symmetrical renal cortical necrosis.

(The uremic syndrome after abortion, especially after neglected criminal abortion, is certainly more common than the sparse number of recorded cases would indicate. Perhaps one of the reasons for this is the hesitancy on the part of physicians to report clinical phenomena which they are unable to explain,—and until recently the whole picture has been a good deal of an enigma. Thus, I remember vividly 2 or 3 of such cases back in the early thirties but they were not published because we were at a loss to know just what was going on. Our best guess was acute nephritis due to a toxin from a hemolytic streptococcal infection, just as occurs sometimes in streptococcal pharyngitis, but this hypothesis could not be established. It seems rather clear now that we were dealing with a renal lesion which is characteristic of a fairly wide generic group and typified by massive tissue damage. Although the patients reported above by Humphrey and Jones retained their mental clarity, it so happened that ours went into uremic coma as the N.P.N. went above 200 mg. per cent. This whole concept has been most helpful perhaps in understanding the oliguria which sometimes attends and follows abruptio placentae. As a case in point may be taken the fatality reported by Young and Walker of London in the J. Obst. & Gynaec. Brit. Emp., 54: 196–202, 1947, and abstracted in the December, 1947 issue of the Survey, p. 643. Here, changes in the uterus resembling those found in the graver forms of abruptio had been produced by the forcible injection into the birth passages of a mixture of soap and dettol in an effort to bring about abortion. The massive uteroplacental injury so produced was fol-

PRIMARY OVARIAN PREGNANCY

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Primary ovarian pregnancy is reported in a 34-year-old woman, married 16 years, who had 1 child and had had 1 miscarriage 10 years before the present history. In November 1946 she failed to menstruate. In December she began to hemorrhage, passing many clots but no membranes. Dilatation and curettage were done, showing proliferative endometrium but no chorionic villi or decidual cells. Bleeding continued sporadically for 3 weeks.

In January, patient complained of a persistent dull aching sensation in the lower abdomen. Laparotomy was done; a normal uterus, not unduly congested tubes, and the ovaries, distinctly separate from tubes, were removed.

The left ovary was slightly enlarged and partially cystic. The right was globular, 5 cm. in diameter, fairly smooth, with no ruptured areas. Its color was dark reddish brown, the total appearance suggesting an endometrial cyst. Routine sections of the wall of the cyst and of the hemorrhagic mass filling the lumen revealed young chorionic villi. The embryo was not recognized; but serial sections were not made, and Curtis reports early destruction of the ovum within the follicle may occur.

Spiegelberg and later workers have formulated certain criteria for diagnosis of primary ovarian pregnancy: (1) The tube, including the fimbriated end, must be intact and distinctly separate from the ovary, must show no microscopic evidence of pregnancy. (2) The gestational sac must definitely occupy the normal position of the ovary. (3) The gestational sac must be connected with the uterus by the utero-ovarian ligament. (4) Ovarian tissue must be demonstrable at several places in the walls of the sac. These criteria are fulfilled in the present case.

Some writers classify ovarian pregnancies into (1) those in which the ovum is in close relationship with a corpus luteum, and (2) those in which no such relationship can be observed. Possibly in the latter the development of the trophoblast in the follicle has resulted in the destruction and disappearance of the lutein cells.

A more elaborate classification (Stux) lists 4 types: (1) intrafollicular, the most common type, in which the ovum is retained, fertilized, and implanted in the follicle; (2) superficial, implanted on the surface of the ovary in accordance with some furrows or areas of degeneration of the particular ovary; (3) interstitial, in which owing to a tough ovarian capsule the follicle perhaps bursts laterally, the ovum escapes into the interstitial cells, and a sperm enters through the follicle to the ovum lying outside the follicle wall; (4) suprafollicular, in which a blood clot at the opening of the ruptured follicle holds the ovum at its exit, where fertilization and implantation take place.

Because the ovary is more elastic and resilient, the duration of an ovarian preg-

Many patients other than those included in the present series, who presented evidence of endocrine dysfunction, and who were considered quite likely to miscarry, have been treated prophylactically during pregnancy, using the treatment outlined, with excellent results.

(This small series of 27 cases included women who had miscarried from 1 to 3 times previously. If a woman has had 3 successive abortions she is properly to be classed as a habitual aborter, but not the woman who has had 1 miscarriage, and, according to many, not even the one who has had 2 abortions, though there are differences of opinion on this point. Whether or not a woman has had previous abortions, certainly no one will question the value of treating any demonstrable endocrinopathy.

On the other hand, there is much confusion as to the value of organotherapy in cases of genuine habitual aborters, although we all use it in some form or another. Progesterone therapy, from which so much was expected, has been rather disappointing. Many who employ it do so because they would feel culpable if they did not and usually with no great degree of enthusiasm. Others have abandoned its use. Its results are for obvious reasons difficult to evaluate. Combinations of estrogen and progesterone have recently become very popular, perhaps more so than progesterone alone. And now the authors throw the whole endocrine book at the patient by adding also the chorionic gonadotrophic, I suppose because of its supposedly supportive effect upon progesterone. All of the elaborate hormone ritual outlined by the authors is presumably by the hypodermic route, and, without meaning to be uncharitable, the plan is open to the criticisms applying in general to long-continued "shot" therapy, and also to those properly leveled at treatment of the "gunshot" variety. The pregnant woman thus treated is going to be a busy little girl.

I suppose that the authors also combine thyroid with the above composite ritual. I certainly hope so, because many of us believe it is more frequently useful than the ovarian or chorionic gonadotrophes. My own reaction is that if I had to choose between thyroid alone and the authors' plan without thyroid, I would certainly select the thyroid. No one knows the rationale of thyroid therapy when there is no clinical or laboratory evidence of hypothyroidism, and yet there are few experienced gynecologists and obstetricians who do not feel that it is often the factor which turns the trick. One is tempted to believe that it has an improving effect upon the intangible factor of germ plasma quality, although there is not the slightest scientific evidence on this point.

One must not omit the husband in the study of such cases, as is so often done. If all demonstrable factors of either constitutional or endocrine type have been corrected as far as possible, modest thyroid therapy of both husband and wife, empirical as it is, appears to be of genuine value. My own observation has been that the chances of a successful pregnancy are best if the pregnancy is not embarked upon until after the couple have been on the thyroid therapy for 2 or 3 months. Thyroid therapy begun only after the male and female gametes have merged appears to be much less frequently effective.—Ed.)

In this study 12 cases are reported among 13,926 deliveries. Gardner and Middlebrook in a review of 280 cases, found the incidence higher after age 30 and most frequent in first and second pregnancies.

Maternal mortality has been variously reported from 14.3 to 40 per cent, and the fetal mortality 50–80 per cent. There were no maternal deaths in the present group.

In these cases there is usually a history of an acute painful episode which corresponds to the tubal rupture or abortion prior to secondary implantation. Pelvic examination reveals the enlarged softened uterus as found in ectopic pregnancy and the soft-to-firm mass formed by the extra-uterine gestation. Biological tests for pregnancy are positive. In the last trimester the small parts of the fetus are often unusually easy to palpate. There is increased incidence of abnormal positions and presentations, especially transverse presentation. At the expected date, patient will go into a pseudo-labor. If the condition is not recognized, the pains will stop and the fetus may die.

Hysterography has been used in diagnosis. In addition to the injection of an opaque medium into the uterine cavity, attempts have been made to use uterine soft tissue studies, pneumoperitoneograms, and amniography. Criteria useful in diagnosing abdominal pregnancy with roentgenograms include (1) the absence of a uterine shadow without the use of an opaque medium using soft tissue technic and studies; (2) the fetus usually high in the abdomen and (3) in an abnormal position, especially transverse; (4) in the lateral view of the abdomen the fetal parts are just beneath the abdominal wall; and (5) after injection of an opaque medium into the uterine cavity, the fetal parts will be found outside the uterine shadow.

In these 12 cases, ages varied from 19 to 39, averaging 29.4 years. Three had no previous children, 7 had had 2 or less. Four patients had gestations advanced to 4 months, 3 at 5 months, 1 each at 7 and 8 months, and 3 were term pregnancies. Three infants (27.2 per cent) were born alive, 2 at term and 1 at 8 months. Seven were previable or lithopedions, 1 a full term stillbirth, and the other a macerated 7 months infant. Nine of the 12 mothers gave histories suggestive of previous tubal abortion or rupture.

In 4 cases, in early gestations where the fetus had been dead for some time and placental vessels were thrombosed, the placenta was removed. In none of the term or near-term pregnancies was the placenta removed. Two cases developed abscesses. One drained through the original skin incision and after several months improved with no further surgery. The other developed a pelvic abscess which was drained through the cul-de-sac of Douglass by colpotomy, followed by improvement and no sequelae. In all other cases when the placenta was left intact there was apparent absorption and no need for further surgery. None of the cases was drained at original surgery, and no marsupialization was done. Four case reports are given.

Immediate operation as soon as the diagnosis is made involves least risk to the mother. As gestation continues there is also a chance of the fetus dying or being deformed. Some feel that surgery should not be resorted to unless the fetus is

nancy is usually longer than that of a tubal pregnancy. In some cases it has gone to full term, with a living child. In others the result has been a lithopedion. In 38 cases of ovarian pregnancy lasting 7 months or more, 12 resulted in a living infant; in 22 the mo·her lived, and in 8 cases both mother and baby lived. The incidence of true primary ovarian pregnancy is very low. One series of 339 ectopic pregnancies included only 1 ovarian pregnancy. Since there may be early rupture of the sac or early degenerative changes, some cases may not be recognized. 2 figures.

(From the viewpoint of pathology, this case report constitutes an interesting and apparently valid addition to the increasing number of primary ovarian pregnancies on record. However, from a clinical standpoint, almost any reader will quite properly question the justification of the radical operative procedure as stated in the 2nd sentence of the 2nd paragraph. No, there are no omissions in the abstract which might bear on this point, for the original article quite brazenly states that a normal uterus, essentially normal tubes and a presumably normal left ovary (as described) were removed in addition to the affected right ovary. No explanation is given and no apologies offered.—Ed.)

THE DIAGNOSIS AND TREATMENT OF ABDOMINAL PREGNANCY

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Southern Surgeon, **13**: 635–644, (Sept.) 1947

The term abdominal pregnancy describes any gestation which is not predominantly intra-uterine or intra-tubal in its anatomic relationship. In primary abdominal pregnancy, evidence of original intra-uterine or intra-tubal position is absent and the ovary is not involved in the placental site. Observation of decidual reaction on the peritoneum and the not uncommon occurrence of endometriosis do allow the possibility of primary peritoneal implantation, but proved cases are few. Certain criteria must be met: The tubes, ovaries and broad ligaments must have a normal appearance with no evidence of injury; no utero-peritoneal fistula; absence of intraligamentary rupture of the tube or penetration of the space between the broad ligaments by the fimbriated tube ends; a pregnancy related exclusively to the peritoneal surface, with no evidence of secondary implantation.

Secondary abdominal pregnancy, by far more common, is a continuation of gestation in the abdominal cavity following primary nidation in the uterine cavity or tube. In the intraperitoneal type, the gestation sac is formed mainly by inflammatory tissue surrounding the amnion, while in intraligamentary implantation the sac displaces the peritoneum upward as it enlarges.

faces greater handicaps in enduring pregnancy than a white woman of equal economic status. Moreover, negligence in seeking prenatal care and in executing proper medical instruction is a major contributing factor among these people.

Surprisingly enough, 10 (30 per cent) of these patients had some prenatal medical attention. This was administered, for the most part, by a local physician in a rural area. In only one case was there a history of frequent visits to the doctor during gestation. This patient was perfectly well until 24 hours before admission, when the onset of the toxemia was abrupt and most severe. Seven (21 per cent) of the patients had a family history of hypertension. Of particular interest is the patient in Case 5, who had 3 sisters dying of fatal eclampsia.

By summarizing the essential clinical aspects of these fatal cases of eclampsia, a composite picture of the average patient can be created as follows:

If a primipara, the patient is about 19 years of age, Negro (in this area only), and has had at least one convulsion prior to admission. During the few days or weeks preceding admission she has experienced increasingly severe headaches and edema. She may also complain of one of the three following symptoms: recent nausea and vomiting, visual disturbances, or abdominal pain. Physical examination reveals that she has hypertension and generalized edema and is in a comatose condition. Tachycardia and pulmonary edema may or may not be present.

If a multiparous patient, she is about 29 years of age, either white or Negro, and has had the signs and symptoms of pre-eclamptic toxemia during a previous pregnancy. There is one chance in three that she has had a previous attack of eclampsia. She, too, is comatose and demonstrates hypertension and edema. In all probability, she has had convulsions prior to admission.

Both patients will demonstrate a slight increase in blood non-protein-nitrogen and a definite increase in blood uric acid. Total plasma proteins will be reduced, and the albumin-globulin ratio markedly reduced. Death will ensue in about two days.

Anatomic lesions

Liver. The liver is the seat of an important pathological change. The lesion most frequently encountered is a focal hyaline or fibrinoid necrosis of the liver cells, usually, but not necessarily, in the periportal areas.

The most characteristic aspect of this lesion is its variability in extent and severity. At times, it is utterly impossible to demonstrate hepatic necrosis, although its presence cannot be eliminated without study of serial sections of the entire organ. At other times the process is extremely widespread so that viable or normal appearing liver tissue is relatively scarce. Occasionally the disease process may be extremely widespread in one lobe of the liver, while the remainder appears relatively unaffected. Generally speaking, the majority of the cases show an affection between these two extremes.

The nature of these focal hyaline or fibrinoid lesions is of considerable interest. They are characteristically small in size and approximately fill one high-power microscopic field under 440X magnification. Adjacent hepatic cells usually involving three to five cords or more in a periportal area lose their distinct cellular

dead. Here the danger of sepsis is increased, which outweighs the advantages gained by thrombosis of the placental vessels.

At the time of primary operation, complete excision of the placenta may be attempted, marsupialization or partial closure with drainage may be tried, or the placenta may be left undisturbed. The last is much preferred today, the method of choice being to ligate and sever the cord close to the placenta which is left in situ. Only infected cases are drained. (One analysis of maternal mortality showed no deaths where the placenta was not disturbed and no drains were used.)

Usually the placenta is completely absorbed and causes no more trouble. It may possibly, however, undergo necrosis, liquefaction, or calcification, with possible infection, or encapsulation resulting in bowel obstruction. Before any attempt at secondary removal of the placenta is made, unless acute emergency demands immediate surgery, it is best to wait 3–8 months after the original laparotomy, to give the vessels a chance to become obliterated and minimize bleeding.

Emphasis is placed on accurate diagnosis, selection of time to operate relative to patient's condition, and especially handling of the placenta. 2 figures.

FATAL ECLAMPSIA

A Clinical and Anatomic Correlative Study

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This paper represents a summary of all fatal cases of eclampsia which were examined at autopsy in the Department of Pathology, Duke Hospital, during the period 1930 to 1946. During this interval there were 33 necropsies performed in cases of fatal eclampsia. Eight of these patients never had convulsions even up to their exitus; the adjustment of these 8 cases as eclampsia depended upon the finding of focal hyaline or fibrinoid necrosis in the liver with a history of severe toxemia.

The author's figures fail to confirm the fact that primiparous patients are more subject to severe eclamptic toxemia. Seventeen (51.5 per cent) of these patients were primiparas, while 16 (48.5 per cent) had had previous pregnancies. These figures are at considerable variance from those given for eclampsia in general. DeLee reports a ratio of primiparas to multiparas of 3:1, while Stander quotes Hinselmann with a ratio of 6:1. The present author's ratio for fatal eclampsia is 1.1:1. The factor of racial distribution presents itself in this group of patients. Twenty-one of the cases occurred in Negro women; one was Indian. This is probably not evidence of racial susceptibility, but rather reflects the nature of the local population. It cannot be ignored that a gravid Negro woman probably

Stage 3 represents the development of lesions remarkably similar to those of nephrosclerosis. There is a diffuse arteriolo and arteriosclerosis. There are scattered obliterated, hyalinized glomeruli. Occasionally one sees fibrosis beneath Bowman's capsule. Six of these cases are in Stage 3.

Adrenals. The lesions found in the adrenal glands have been a source of great interest and investigation. Essentially they consist of necrosis and hemorrhage of varying degrees. Eleven (33 per cent) of these patients showed this pathologic change in the adrenal glands. Of these, 45 per cent were classified as severe in that practically no functional adrenal cortical tissue remained. The other 55 per cent showed involvement of approximately half of the cortical tissue. There were no cases with minimal lesions. In summarizing the adrenal changes, it appears that there is a possible relationship between the adrenal damage and the terminal appearance of the shocklike syndrome. In the light of the many widespread lesions in other viscera, it would be gross misinterpretation to say that the sole cause of death was adrenal insufficiency. However, it does appear that adrenal insufficiency secondary to recent widespread injury may be a contributing factor in the exitus of certain patients.

Additional Lesions. The lungs showed pneumonia of varying degrees in 16 of the cases. These infections were usually marked by pulmonary edema which failed to respond to the usual therapy. An associated purulent bronchitis was present in 4 of these cases. Of considerable clinical interest was the presence of unrecognized bilateral hydrothorax: Case 13, 550 c.c. and 450 c.c.; Case 16, 1,000 c.c. and 1,000 c.c.; Case 19, 550 c.c. and 500 c.c.; Case 27, 300 c.c. and 200 c.c.; Case 28, 700 c.c. and 450 c.c. Whether the removal of such fluids would have altered the outcome is highly debatable.

The heart was the site of hemorrhage in twelve patients. Four of these showed focal necrosis of the myocardium with slight cellular reaction. There were two cases of myocarditis, one characterized by the focal aggregation of polymorphonuclear leucocytes, and the other by a diffuse scattering of round cells. There was one case of focal acute endocarditis.

Focal necrosis of the brain was present in one case. Cerebral hemorrhage was also present in three cases. In two this hemorrhage was massive. These two cases, as well as two others showed cerebral arteritis and arteriolitis with necrosis of the vessel walls.

On the basis of his findings the author believes it reasonable to postulate, as Dexter and Weiss have suggested, the following sequence of events in eclampsia: a vasoconstriction occurs with a resulting hypertension which leads to small arterial and arteriolar changes; these vascular changes, together with local tissue hypoxia, result in the petechial hemorrhages and the focal necroses. The lack of change in the precapillary arterioles in the author's Stage 1 of the renal lesion is in accord with this hypothesis.

(This paper has been abstracted at length because it reports the first comprehensive study of the pathology of eclampsia to appear for many years. The sum and substance of the findings are in keeping with current thought in regard to the underlying mechanism of eclampsia, namely that it is a disease of the smaller arterioles characterized by vasospasm

outline and take on a brighter and lighter hue with the eosin. Their nuclei have disappeared, and the cell borders seem to run together without a definite line of demarcation. There may or may not be hemorrhage in the immediately surrounding area. The amount of hemorrhage has not been very impressive in these cases, although it is frequently found beneath the liver capsule without any apparent associated hyaline necrosis. When it does occur deep in the liver substance, it is usually extensive and macroscopically visible.

Kidney. The glomeruli are usually avascular and devoid of erythrocytes, although at times they may be the seat of acute congestion. Congestion is evident when there is pronounced heart failure and accompanying congestion of all the abdominal viscera. Congestion may also be seen occasionally when septicemia is present. There is also a definite increase in the endothelial cells in the glomerulus, as indicated by the increase in nuclei present. Also, one may see fibrinoid or hyaline necrosis of a glomerular tuft, which may spread to involve the entire glomerulus. The capillary basement membrane is conspicuously thickened and may even be duplicated. In the preglomerular arteriole there is swelling of the wall, which may then undergo necrosis or hyalinization. If it be necrosis, there is usually thrombus formation which may extend further into the glomerulus itself.

The author has not been impressed by the tubular changes. It is true that there is cloudy swelling and some colloid degeneration of the tubular epithelium, but this is a highly nonspecific reaction and is seen in a wide variety of disease processes. Emphasis in the past has been placed on the presence of fat droplets within the tubular epithelium. Fat stains have been performed upon a number of these sections, and the presence of fat has been demonstrated. However, it is far less prominent than is usually seen in chronic glomerulonephritis. Indeed, in some of these sections the fat was more prominent in the glomeruli than it was in the tubular epithelium.

All of the changes described above are qualitative in nature and represent progressions of the same underlying pathologic process. To the author's knowledge no one has attempted to estimate these lesions quantitatively. Therefore, since it appeared to him that the renal changes fall into three general groups, he has established three stages which he thinks represent progressive degrees of kidney damage in eclampsia.

Stage 1 represents the earliest level of renal damage. It is characterized by the presence of usually avascular glomeruli with an increase in the glomerular nuclei. There is usually moderate thickening of the capillary basement membrane. In this stage there is no thickening of the arteriolar wall. Of these 33 fatal cases, 11 fall into this group.

The essential difference between Stages 1 and 2 is the finding in the latter group of thickening of the arteriolar wall. It has been suggested that this early change may be attributable to edema. There may or may not be fibrinoid changes in the glomeruli. If the fibrinoid changes are evident in the glomeruli, there is usually an involvement of the arteriole, as well. Sixteen of our cases are in this group.

stroma. Although the A-Z reactions I, II and III in the urine had been negative at the time of the first examination, all histological data indicated the existence of a malignant chorionepithelioma. Consequently a repetition of the A-Z test was waived and a laparotomy was immediately performed. The uterus and adnexa were removed.

The uterus measured 15 x 10.5 x 7 cm. The ovaries were the size of a hen's egg and showed numerous cysts on both sides, of which the majority were filled with serous fluid and some with blood. Lutein cell tissue was not visible to the naked eye in the walls. The uterine cavity was filled with soft, partly disintegrated red to red-brown neoplastic tissue which had invaded the muscle and, on the left side, had reached the subserous layer. In the fundal region it had penetrated the anterior wall of the uterus and the only remains of smooth corpus mucous membrane were on the right side above the internal os. The tumor was diagnosed as a chorionepithelioma with extensive necroses and destructive deep growth, combined with a cystic transformation of the ovaries.

An X-ray examination of the lungs following the operation showed four round shadows, each the size of a pea, having the appearance of metastases. The hormone test showed 25,000 mouse units of gonadotrophic hormone in one liter of urine. The patient was discharged but returned three times at intervals of four weeks for ambulant roentgen ray treatment of the lungs. After the second treatment the round shadows in the left lung had diminished considerably and the A-Z reactions were negative. After the third application of the rays, the metastases in the lungs had completely disappeared and the A-Z reaction was again negative. A final checkup nearly a year later revealed a complete cure.

In spite of these negative results in the case described, the author considers that the A-Z reaction should be employed as an aid to diagnosis, and he also stresses the value of the quantitative hormone examination as especially valuable in differential diagnosis and prognosis. The higher the hormone content of the urine, the more likely the presence of a chorionepithelioma. A further diagnostic aid is the examination of tissue excised by means of the implantation method. If small bits of suspected tissue taken from the portio and detoxified with ether produce the A-Z reactions II or III the diagnosis is clear.

In normal pregnancy the hormone content of the urine is 50–30,000 mouse units per liter of urine, and the secretion of hormone ceases within 14 days at the most after expulsion of the conceptus. A positive A-Z reaction four weeks after delivery or abortion should indicate the existence of a chorionepithelioma if a new pregnancy is out of the question. But when a hydatidiform mole exists the hormone secretion may continue for weeks or months, and be as high or even higher than in chorionepithelioma, and the diagnosis can only be determined if the rise of the hormone content in the urine can be determined by quantitative analysis. However, the A-Z reaction is undoubtedly of value in the detection of reactivation and metastasis. If it is negative after a month and remains so, the prognosis is favorable, but if there is a positive reaction, reactivation or metastasis must be reckoned with at once.

In some cases in which the histological findings are negative or doubtful a cor-

and subsequent alteration in the vessel wall if the vasospasm lasts long enough. In regard to the hepatic changes long thought to be pathognomonic of eclampsia, it is apparent from this study and others that these are not at all constant in this disease and when present are presumably the result of the vascular process.—Ed.)

MALIGNANT CHORIONEPITHELIOMA OF THE UTERUS WITH PULMONARY METASTASES AFTER DELIVERY AT TERM AND NEGATIVE ASCHHEIM-ZONDEK REACTION

P. Schugt

Solingen, Germany

Two important aids in the diagnosis of malignant chorionepithelioma are histopathological examination and the Aschheim-Zondek reaction. Observations with the latter procedure are still not extensive, however, and further data are desirable. The following case in which such a diagnosis, following term delivery, was confirmed despite a negative A-Z reaction, would seem to justify the author's conclusion that laboratory findings cannot completely replace clinical observation and experience.

The case was that of a 25 year old woman who gave birth to a healthy child delivered by forceps. A week later she suffered a hemorrhage, followed by a curettage performed by the accoucheur. Three weeks after the curettage she was admitted to the Municipal Hospital at Solingen, Germany, after recurrent hemorrhages had been treated medicinally without success.

Examination showed an enlarged uterus. The adnexa were apparently unaffected and the internal organs were normal. A curettage was performed whereby some fragments of tissue consisting of polymorphonuclear syncytial cell formations, with no Langhans cells, were obtained. Some portions of the tissue were necrotic, but no typical decidua or fetal villi were found. From these specimens it could not be determined whether the alterations in the tissue were merely degenerative changes in old decidual elements, or whether they pointed to the existence of a chorionepithelioma. Further supervision was indicated and the patient returned a month later for a second examination. Meanwhile she had suffered from pains in the lower abdomen and attacks of vomiting and had lost 3 kilos in weight.

The uterus was still enlarged and a lump the size of a plum was found at the base on the left. A second curettage yielded bits of tissue from the corpus uteri similar to the syncytial cell masses obtained from the previous curettage. There were many amitotic divisions, giant cells with one or several nuclei and sporadic atypical mitoses. Other cells had large, vacuolated nuclei. Many fragments of tissue were necrotic, and here and there the cellular masses had penetrated the

The lowest dosage employed in these treatments was 600,000 units of penicillin, 10,000 units every 3 hours for 60 doses. Later the dosage was increased and in some arsenoxide was added.

Follow-up after treatment included monthly examinations with quantitative STS for 2 years. An STS was done on the baby at 1 week and monthly till 16 weeks, or preferably for a year, if the results were negative. If positive, the STS was repeated weekly until negative or until the diagnosis of congenital syphilis was established. A baby was considered non-syphilitic if at 16 weeks there were no clinical evidences of syphilis and the STS and x-rays of the long bones were negative.

The 287 patients may be studied in 3 groups: group 1, the 177 patients treated during pregnancy; group 2, the 84 treated prior to pregnancy; group 3, 26 who relapsed or were reinfected, 3 prior to and 23 during pregnancy, and were re-treated.

In the first group there were 123 cases of early infectious syphilis and 54 latent syphilis. Non-syphilitic babies resulted from 137 pregnancies, plus 20 probably non-syphilitic followed less than 16 weeks. There were 10 abortions or premature deliveries, not caused by syphilis. Thus 167 pregnancies, 94.4 per cent, had non-syphilitic end results.

There were 4 cases of congenital syphilis (2.8 per cent), 2 from mothers with early infectious syphilis who received 1,200,000 units of penicillin, 20,000 units every 3 hours for 60 doses during the antepartum period, and 2 from mothers with latent syphilis. One of the latter received 1,200,000 units of penicillin, 40,000 every 6 hours for 30 doses, beginning in the 26th week of pregnancy. The other received 4,800,000 units, 53,333 every 2 hours for 90 doses, starting at 30 weeks. The end result in this case was surprising; if a further period of observation of the baby without therapy had been permitted, gradual improvement and cure from intrauterine therapy might have resulted.

Six others ended in late abortions or neonatal death. Syphilis was probably the cause. In all 177, then, syphilis was the definite or possible cause of a bad result in 10 cases, 5.6 per cent. Another infant acquired syphilis between 7 and 17 weeks, when the mother relapsed or was reinfected.

The 84 mothers who were treated 1–20 months prior to pregnancy had no additional therapy during the prenatal period. The single case of congenital syphilis (1.2 per cent) resulted from an unobserved relapse in an uncooperative patient. It seems no longer necessary to retreat every syphilitic pregnant woman during each pregnancy since the advent of penicillin, provided the patient will return for thorough examination and quantitative STS at least monthly.

Of the 26 relapses or reinfections, 3 occurred prior to pregnancy and 23 during pregnancy; 3 followed arsenoxide and fever, the remainder coming after initial penicillin therapy. Nearly half of the few receiving 600,000 units relapsed. Following retreatment, no cases of congenital syphilis were encountered. Twenty of the babies were definitely non-syphilitic and 3 probably non-syphilitic. Three results (11.5 per cent) were considered possibly due to syphilis—2 abortions and 1 32-week stillbirth.

rect diagnosis may be obtained through a positive reaction from the A-Z reaction. On the other hand, where the result is negative and the quantitative hormone analysis gives a positive result, an operation should be performed without resort‍ing to a test curettage which might bring about a metastatic spread of the tumor.

Many explanations have been given for negative results of hormone tests. The size or the histological structure of the chorionepithelioma, especially the fact that syncytial elements are not present in sufficient quantities, may be respon‍sible. Thus, in the later months of normal pregnancy a positive reaction occurs when there are no Langhans cells and hence the presence of syncytial cells would seem to be of greater importance in the reaction. A chorionepithelioma or a hy‍datidiform mole may be cut off from the uterine circulation through degenerative processes, extensive thromboses and necroses, blood coagulation and fibrin, whereby a negative reaction is produced. Further quantitative hormone tests have shown that in the transition from hydatidiform mole to chorionepithelioma, the hormone secretion follows a curve which has a negative phase.

THE RESULTS OF PENICILLIN THERAPY FOR SYPHILIS IN PREGNANCY

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Ideal antisyphilitic therapy during pregnancy should include (1) freedom from serious toxic reactions, (2) permanent cure of the maternal disease, (3) adequate therapy in a short treatment period, (4) prevention of transmission of the disease from mother to baby, and (5) cure of congenital syphilis via the placenta where the disease has already been transmitted. Penicillin best fulfills these require‍ments.

No serious toxic reactions occur with penicillin. Urticaria was not encoun‍tered in any of the 252 pregnant patients treated for early infectious syphilis. Of the 82 who had arsenoxide also, 15 complained of vomiting following the arsenical.

Several investigators have reported uterine contractions with penicillin ther‍apy, possibly resulting in abortion or premature delivery, though others have felt this could be avoided by reduction in dosage during the first 48 hours. In a series of 156 cases reported from the Bellevue Rapid Treatment Center, no instance of abortion or premature labor was encountered attributable to penicillin therapy. In the present group of 177 who received penicillin treatment during pregnancy, abortions or premature deliveries occurred in 10.7 per cent; Goodwin and Moore also found the incidence of abortion during penicillin therapy less than that ex‍pected normally.

The lowest dosage employed in these treatments was 600,000 units of penicillin, 10,000 units every 3 hours for 60 doses. Later the dosage was increased and in some arsenoxide was added.

Follow-up after treatment included monthly examinations with quantitative STS for 2 years. An STS was done on the baby at 1 week and monthly till 16 weeks, or preferably for a year, if the results were negative. If positive, the STS was repeated weekly until negative or until the diagnosis of congenital syphilis was established. A baby was considered non-syphilitic if at 16 weeks there were no clinical evidences of syphilis and the STS and x-rays of the long bones were negative.

The 287 patients may be studied in 3 groups: group 1, the 177 patients treated during pregnancy; group 2, the 84 treated prior to pregnancy; group 3, 26 who relapsed or were reinfected, 3 prior to and 23 during pregnancy, and were retreated.

In the first group there were 123 cases of early infectious syphilis and 54 latent syphilis. Non-syphilitic babies resulted from 137 pregnancies, plus 20 probably non-syphilitic followed less than 16 weeks. There were 10 abortions or premature deliveries, not caused by syphilis. Thus 167 pregnancies, 94.4 per cent, had non-syphilitic end results.

There were 4 cases of congenital syphilis (2.8 per cent), 2 from mothers with early infectious syphilis who received 1,200,000 units of penicillin, 20,000 units every 3 hours for 60 doses during the antepartum period, and 2 from mothers with latent syphilis. One of the latter received 1,200,000 units of penicillin, 40,000 every 6 hours for 30 doses, beginning in the 26th week of pregnancy. The other received 4,800,000 units, 53,333 every 2 hours for 90 doses, starting at 30 weeks. The end result in this case was surprising; if a further period of observation of the baby without therapy had been permitted, gradual improvement and cure from intrauterine therapy might have resulted.

Six others ended in late abortions or neonatal death. Syphilis was probably the cause. In all 177, then, syphilis was the definite or possible cause of a bad result in 10 cases, 5.6 per cent. Another infant acquired syphilis between 7 and 17 weeks, when the mother relapsed or was reinfected.

The 84 mothers who were treated 1–20 months prior to pregnancy had no additional therapy during the prenatal period. The single case of congenital syphilis (1.2 per cent) resulted from an unobserved relapse in an uncooperative patient. It seems no longer necessary to retreat every syphilitic pregnant woman during each pregnancy since the advent of penicillin, provided the patient will return for thorough examination and quantitative STS at least monthly.

Of the 26 relapses or reinfections, 3 occurred prior to pregnancy and 23 during pregnancy; 3 followed arsenoxide and fever, the remainder coming after initial penicillin therapy. Nearly half of the few receiving 600,000 units relapsed. Following retreatment, no cases of congenital syphilis were encountered. Twenty of the babies were definitely non-syphilitic and 3 probably non-syphilitic. Three results (11.5 per cent) were considered possibly due to syphilis—2 abortions and 1 32-week stillbirth.

Total results are thus 95.2 per cent non-syphilitic, 1.7 per cent definitely syphilitic, and 3.1 per cent possibly syphilitic, for the 287 cases.

Non-syphilitic babies can be obtained even when treatment is given a short time before delivery. In 1 patient delivery occurred 2 days after completion of penicillin therapy (1,200,000 units); the baby was non-syphilitic after 1 year's follow-up. Another (not included in this study since she received only 180,000 units prior to onset of labor) delivered twins at term who were non-syphilitic through a year following.

All but 1 of the 10 bad results due or possibly due to syphilis occurred in patients treated after the 16th week of pregnancy. However, 5 of these are late abortions or prematures, and the diagnosis "possibly due to syphilis" may be wrong. Healthy offspring are consistent with positive STS in the mother at the time of delivery, although congenital syphilis or treatment failures are more likely where the mother's STS reveal relatively high titers.

Any definite rise in the titer is an indication for retreatment, while a progressive decline in STS, much slower in treatment of latent syphilis than in early infectious stages, indicates satisfactory response. Decisions regarding therapy must be made where the value of the STS remains stationary or declines relatively slowly and irregularly. In patients treated prior to or during pregnancy, when the quantitative Kahn (Bellevue Hospital Rapid Treatment Center) is 16 or higher without evidence of a previous rapid drop, the patient should be retreated. A value of 8 is questionable but probably does not call for treatment, while 4 is satisfactory.

A dosage of 4,000,000 units of penicillin in distilled water, 40,000 units every 3 hours for 100 doses, is being used at present. An evaluation is in process of penicillin in beeswax and oil, 600,000 units daily for 8 days, a total of 4,800,000 units. A total dosage of less than 2,400,000 units is most probably inadequate. 4 tables.

PRENATAL SYPHILIS; ITS PREVENTION BY USE OF PENICILLIN IN TREATMENT OF PREGNANT WOMEN WITH EARLY INFECTIOUS SYPHILIS

Hans C. S. Aron, Robert L. Barton and Theodore J. Bauer

From the Chicago Intensive Treatment Center, Venereal Disease Control Program, Chicago Board of Health, in cooperation with the United States Public Health Service

Transmission of syphilis to the fetus occurs much more frequently when pregnant women have syphilis in the early infectious stages than in later stages. The effect of any therapy in preventing prenatal syphilis may therefore be best eval-

uated by its effect on the children of mothers who during pregnancy had indisputable early infectious syphilis.

When rigidly selected, the number of patients seen who had proved early infectious syphilis was limited. Goodwin and Moore (J. A. M. A., 130: 688, Mar. 16, 1946) have compiled results of penicillin in such cases in their "Baltimore group" of 31 women with infectious syphilis during pregnancy (33 infants), and 26 women (27 infants) from the "Philadelphia group." To these 57 women with 60 infants may now be added 36 mothers and infants from the Chicago Intensive Treatment Center.

All mothers observed in this project presented lesions of early infectious syphilis, and the presence of syphilis was confirmed by dark field examination in all cases, except for 1 in which there were lesions indubitably characteristic of secondary syphilis but unsuitable for dark field examination. The infants were born not more than $7\frac{1}{2}$ months after diagnosis of syphilis and beginning of penicillin therapy. No other antisyphilitic agents were given, and the intensive course of penicillin was not repeated unless there was serologic or clinical evidence or relapse.

Comparison is also made with a group of 28 infants of 28 women with infectious syphilis during pregnancy who, before the advent of penicillin, had received intensive arsenotherapy (treatment described by Eagle and Hogan, that of Schoch, or fever chemotherapy; Bundesen, Bauer, and Kendall, J. A. M. A., 123: 816, Nov. 27, 1943). These patients came from the same socioeconomic and racial backgrounds as the Chicago penicillin group, and were selected for early infectious syphilis by the same criteria.

Of the 36 infants delivered of mothers treated with penicillin exclusively, 1 died of prolapse of the cord and asphyxia, an accident hardly attributable to syphilis or to the therapy. A second infant was reported stillborn. The mother of this infant had secondary syphilis 7 weeks before delivery and was treated with 2,400,-000 units of penicillin over a 15-day period. Relapse was demonstrated 1 month after delivery, requiring retreatment with 4,800,000 units.

No signs of symptoms of congenital syphilis could be detected in the 34 living infants by thorough physical examinations, serologic tests, or roentgenologic studies of the long bones. Three of the 34 were reported possibly premature—an incidence of 8.8 per cent. (A recent 15-year study in Philadelphia established the average incidence of premature infants at 9.4 per cent.) No case of abortion or miscarriage was reported in this series of mothers treated with penicillin during pregnancy.

The results for the Chicago group agree perfectly with those from Philadelphia and Baltimore. For the 3 groups, there is a total of 96 infants, 1 with congenital syphilis and 1 stillborn—an over-all incidence of failure to prevent prenatal syphilis of 2.1 per cent. An incidence of 15 per cent congenital syphilis after intensive arsenotherapy has been calculated by Goodwin and Moore.

For the strictly comparable Chicago groups alone, there was failure to prevent congenital syphilis in 1 (stillborn, possibly because of syphilis), or 2.8 per cent, among the penicillin group, and 3, or 10.7 per cent in the group receiving arseno-

therapy.   The 59 infants free from infection were followed for at least 2 months
and in most cases up to a year.   Treatment was started when the majority of pa-
tients in both groups were 16–32 weeks pregnant.

Observations indicate that treatment with penicillin during pregnancy may
prevent prenatal syphilis, even though the mother is not cured and subsequently
relapses.   In the Philadelphia and Baltimore groups normal infants were born of
mothers who relapsed after treatment with penicillin, including 3 who had sero-
logic relapses in the last trimester of pregnancy and were retreated.   In 2 Chicago
cases the mothers had mucocutaneous relapses (spirochetes revealed on dark field
examination) after treatment with penicillin and yet the infants remained free of
syphilis.   It has been shown recently that penicillin given to pregnant women
passes to the fetus in relatively large quantities as early as the tenth week of gesta-
tion.   Apparently the amount transmitted may be sufficient to protect or pos-
sibly cure the fetus, even though the amount of penicillin in the mother's blood
fails to eradicate the maternal infection.

Of the various drugs used in intensive treatment and designed to prevent pre-
natal syphilis, penicillin is unexcelled and may be used with safety to both the
mother and the fetus.   4 tables.

APPENDICITIS COMPLICATING PREGNANCY, LABOR
AND THE PUERPERIUM

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The management of acute appendicitis during the first 7 months of pregnancy
is well established, namely, early diagnosis and immediate appendectomy.   How-
ever, the best form of treatment during the last trimester—especially the prefer-
able type of surgical and obstetrical procedures to be used—has been the subject
of considerable divergence of opinion.   A number of authors have recommended
that appendectomy be accompanied by cesarean-hysterectomy during the last
trimester on the grounds that the process of labor, if it follows shortly, may break
down protective adhesions with dissemination of infection throughout the peri-
toneal cavity.   Uterine intervention has been advised particularly if perforation
or abscess formation has occurred.   On the other hand, a number of authorities
take the opposite point of view, regarding the above threat as more theoretical
than real.   Thus, Cosgrove has reported 18 cases of appendicitis in pregnancy
in several of which labor followed very shortly after removal of a perforated, gan-
grenous appendix but despite this the postoperative courses were uneventful.
(Am. J. Obst. & Gynec., 34: 469, 1937).

For the purpose of studying this question further, Meiling has reviewed 26

cases of appendicitis in pregnancy which were observed at the University Hospitals of Cleveland between 1934 and 1946 inclusive. In this series 84.6 per cent of the patients developed acute appendicitis during the first 6 months of gestation. The abortion rate was 26.1 per cent, the fetal and neonatal mortality rate (including abortions) was 34.6 per cent and the maternal mortality rate 7.69 per cent (2 cases).

Four case histories are presented in detail attesting difficulties which sometimes surround the diagnosis of appendicitis in pregnancy; these bear also on the question of the management of the condition late in gestation.

The first case was that of a 27 year old secundipara who was admitted to the hospital near term in acute distress complaining of severe abdominal pain accompanied by nausea and vomiting. There was a history of an episode of acute lower abdominal pain during the 6th month of gestation but bed rest and sulfadiazine therapy had resulted in complete recovery. On the present admission the uterus remained very tense, there was generalized abdominal tenderness and the tentative diagnosis of placental separation with retroplacental hematoma and intrauterine hemorrhage was made. A secondary diagnosis of twisted, gangrenous ovarian cyst was considered. When the abdomen was opened through a low midline incision, purulent exudate was encountered. Transverse laparotrachelotomy was performed. followed by appendectomy. Subsequent pathological report on the appendix showed acute suppurative appendicitis. Ten grams of sulfathiazole crystals were placed in the peritoneal cavity and postoperatively the patient received 100,000 units of penicillin q.4 h. intramuscularly for 7 doses followed by 20 doses of 50,000 units each, a total of 1,700,000 units. A Levine tube with gastric suction was used for 72 hours. After a very smooth postoperative course, the patient and baby were discharged well on the 10th postoperative day.

In the second case, the patient, Para II, experienced shaking chills 6 hours after a normal delivery accompanied by pain in the right flank radiating to the right costovertebral angle. The temperature was 39.5° C. The abdomen was markedly distended but there was no rebound tenderness. However, a bulging of the right abdominal wall over the crest of the ileum could be seen. A primary diagnosis of paranephritic abscess on the right was made and a secondary diagnosis of possible acute appendicitis with perforation and peritonitis. After 30 hours of observation, operation was performed and a retroperitoneal abscess of the right abdominal wall was drained of 500 cc. of thick, purulent exudate. At the base of the abscess cavity the cecum and edematous appendix could be visualized. The peritoneum was not entered. The cavity was drained and postoperatively the patient was given sulfadiazine intravenously and 30,000 units of penicillin intramuscularly. The patient was ambulatory on the 17th postoperative day and discharged on the 21st day.

The third and fourth cases were not included in the 26 mentioned above because they occurred at other hospitals. In the former of these—a fatal case—the patient, Para IV, was admitted to the hospital with labor well established. During the 6th month of pregnancy the patient had been admitted to the hospital for 36 hours complaining of vague right upper quadrant pain, but there was no

nausea, vomiting or temperature elevation. Labor, terminated by elective low forceps, was normal. On the first postpartum day the patient developed abdominal distention, with temperature elevation of 38 C. and complained of generalized abdominal pain. Nausea and vomiting followed on the second day with continued distention and temperature of 39.3 C. Treatment consisted of enemas, prostigmine, penicillin (100,000 units followed by 30,000 q. 3 h. for 4 doses), intravenous fluids and gastric suction started on the 3rd day. After temporary improvement, during which penicillin and suction were stopped, the patient had a chill on the 5th day, went into shock and died 18 hours later. Autopsy showed acute gangrenous appendicitis with perforation and diffuse acute fibrinopurulent peritonitis.

In the 4th case the patient, Para O, was delivered by elective low cervical cesarean section because of outright pelvic contraction. Symptoms and signs of appendicitis developed on the 8th postoperative day, followed promptly by operation, chemotherapy and rapid recovery.

The author points out that these 4 cases exemplify the various ways in which acute appendicitis occurring during late pregnancy, labor or the puerperium may be masked. (In the first case the preoperative diagnosis was abruptio placentae and in the second paranephritic abscess; in the third case, as the author emphasizes, the diagnosis was not made at all, the clinical picture suggesting, presumably, puerperal infection. Hence, the prostigmine and enemas.—Ed.)

In regard to the management of acute appendicitis, with or without perforation, during the last 2 months of pregnancy the author believes that the following treatment warrants consideration: cesarean section by low transverse laparotrachelotomy, followed by properly executed appendectomy, intraperitoneal implantation of 5 to 10 grams of sulfanilamide or sulfathiazole crystals, massive doses of penicillin postoperatively for several days accompanied by gastrointestinal decompression, blood and plasma transfusions and intravenous nutrition.

(Although the author cites a certain body of opinion in support of the treatment he recommends, I imagine that the majority of obstetricians (including myself) would be decidedly opposed to the cesarean section part of this regime. To incise the uterus and lay bare the placental site through a peritoneum covered with pus, as was done in the first case abstracted above, is such a flagrant violation of all surgical and obstetrical principles that it would strike almost anyone as out of the question. It is true that the patient enjoyed an eminently satisfactory convalescence, but this I would regard as a triumph of chemotherapy rather than one of good judgment. This is the only case in the author's series delivered by the abdominal route; the fourth case, abstracted above, which occurred in another hospital and in which appendicitis developed 8 days after cesarean, has nothing to do with the present problem. On the other side of the question, that is, if the near-term uterus is left untouched in the course of appendectomy, there is of course the threat of some catastrophic breakdown of adhesions if labor follows within the next few days, as it often does. What evidence is there to document this fear? In my opinion, very little. Like Cosgrove, we have seen a number of patients near term with acute appendicitis who went into labor a day or two after appendectomy but nothing untoward happened. In Meiling's own series there is only one case, No. 22, which may possibly support this fear that labor immediately after appendectomy is dangerous, but few details are given and he does not cite it as evidence. In this instance, a 38-year old woman, Para IX, 6½ months pregnant, was operated upon for suppurative appendicitis, underwent spontaneous delivery of a stillborn on the 2nd postoperative day and died the next day. Whether the picture suggested

breakdown of a protective wall of adhesions is not stated, but even if so, it should be noted that the patient was only 6½ months pregnant and would scarcely come under the regime of therapy recommended.

All in all, the evidence presented in this series of cases in favor of cesarean before appendectomy in late pregnancy, would seem to be very slim. Not only for this reason does the author's recommendation in regard to abdominal delivery seem to me regrettable, but also because the journal in which the article appears reaches a huge number of general surgeons, with implications which are plain enough.

The author's emphasis on the difficulties which sometimes hamper and delay the diagnosis of acute appendicitis in late pregnancy and the puerperium is well taken and timely. In this connection it may be recalled that two important abdominal wall signs of appendicitis, muscle rigidity and rebound tenderness, may be entirely absent at that time owing to the extreme laxity of the musculature. Moreover, a number of rather common obstetrical complications may lead one astray, such as abruptio and degenerated myoma in pregnancy, and, of course, puerperal infection in the puerperium. Appendicitis with fulminant peritonitis, when developing shortly after delivery, may even simulate postpartum shock, as was observed in one of our own fatal cases. Finally, as Meiling emphasizes, acute appendicitis in late pregnancy is rare, so that the mathematical chances are usually against the man who holds out for this diagnosis.—Ed.)

HODGKIN'S DISEASE AND PREGNANCY

REVIEW OF THE LITERATURE AND REPORT OF A CASE

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The Grace Hospital Bulletin, 25: 27–34, January, 1947

The author prefaces this case report by an extensive review of the literature. Some of the more accessible articles may be epitomized as follows. Gemmel of London, England, discusses 6 cases of pregnancy complicated by Hodgkin's disease. In one the disease was diagnosed at 4½ months' duration of the patient's second pregnancy. X-ray therapy, arsenic and extract of lymphatic gland were administered and she was delivered of a normal full term infant. Following the birth of her second child she became pregnant on 2 or more occasions and delivered normal full term infants each time. Early in each of the pregnancies, she developed cervical lymphadenopathy and was given x-ray therapy, extract of lymphatic gland and strychnine. He records 5 other cases but gives no details. No mention is made of any untoward effect on the offspring. (J. Obst. & Gynec. Brit. Emp. 30: 373, 1923).

Bethel and his associates present 3 cases of Hodgkin's disease complicated by pregnancy. In 2 of these the pregnancy caused aggravation of the process. One mother died of Hodgkin's disease 3 years after delivery, 1 nine years, and a third is living 4 years after delivery. The 3 offspring were normal when examined at 18, 15 and 4 years of age respectively. (Arch. Int. Med. 77: 92–99, Jan., 1946).

Kushner presents a case in which the diagnosis of Hodgkin's disease was made in the 14th month after the birth of the 2nd child. Roentgen therapy was administered and during the course of treatment she was discovered to be pregnant. Ten and a half months after the diagnosis of Hodgkin's disease and 9½ months after the x-ray therapy was begun, she was delivered of a normal 2778 gram, living, female child. During the 2 years following the birth of the 3rd child she continued to receive x-ray therapy, but ran a downhill course and expired 2 years and 9 months after the diagnosis of Hodgkin's disease and 1 year and 10 months after the birth of her 3rd child. Follow-up studies on the child, up to the age of 2½ years, showed a normal development for her age. (Am. J. Obst. & Gynec. 42: 536, 1941).

Klawans cites a case in which Hodgkin's disease manifested itself in the 24th week of pregnancy as a chain of enlarged cervical glands which doubled in size in 2 weeks and was accompanied by an enlargement of the inguinal and cervical chains. X-ray therapy was instituted. The glands continued to enlarge and a marked edema of the vulva developed. A cesarean section was performed 9 weeks after the clinical diagnosis and 4 weeks after the pathological diagnosis of Hodgkin's disease was established. A female infant weighing 3118 grams was delivered. Massive Roentgen therapy was then started but the mother became progressively worse and expired 11 weeks after the first clinical manifestation of the disease was noted and 45 days postpartum. (Am. J. Obst. & Gynec., 43: 895, 1942).

Wolff and Limarzi present two cases of pregnancy, 1 complicated by Hodgkin's disease and the other complicating Hodgkin's disease. The first is a 20 year old gravida 1, para 0, in which cervical lymphadenopathy was noted in the early part of the 4th month of her pregnancy. Biopsy and pathologic study revealed Hodgkin's disease. Pregnancy was uneventful. In her 36th week she was delivered of a 2550 gram female infant. She ran a progressively downhill course. The second case is that of a 32 year old gravida 1, para 0, who was well until 27 years of age at which time biopsy and pathologic study of enlarged cervical and axillary glands revealed Hodgkin's disease. Roentgen therapy was instituted 4 years later. The following year she became pregnant and was delivered of a 2430 gram healthy infant following an uneventful pregnancy and normal labor. Following the delivery the course was progressively downhill. (Am. J. Obst. & Gynec. 51: 447, 1946.)

Priesel and Winkelbauer record the case of a 31 year old pregnant woman with proven Hodgkin's disease of one year's duration who gave birth to a normal living child. She died of the disease several weeks following delivery. Three and one-half months later the child expired and autopsy and pathologic study revealed involvement of all the organs.

The above case report and one report from Italian sources are the only ones which suggest that the infant may occasionally be afflicted with Hodgkin's disease.

The present author reports the following case:

On October 2, 1939, a 20 year old colored female, gravida 3, para 2, reported to the Grace Hospital Tumor Clinic. Her chief complaint was of a swelling in

the right side of her neck which she noticed one week previously. No history of previous lymphadenopathy could be elicited. Examination of the neck revealed a small, firm, nontender, freely movable nodule which was oval in shape and measured about 1.5 cm. by 1 cm. in size and was located in the upper portion of the right anterior cervical chain. On the right side of the neck 2 small, nontender, cervical nodes, about 1 cm. in length could be palpated in the anterior triangle. The white blood count was 5300 with 63 per cent polymorphonuclear cells.

On October 16, 1939, the gland in the right anterior triangle was removed and the pathological report of the section, established by C. I. Owen, was Hodgkin's disease. Between November 18, 1939 and December 5, 1939, the patient received 13 Roentgen ray irradiations to the cervical, axillary and inguinal regions totalling 2464 R units. On March 5, 1940 she received an additional 22 R units to the upper one-half of her body.

The blood picture varied as follows: red blood cells from 3,500,000 to 4,120,000; hemoglobin 12 grams to 14 grams; white blood cells 2900 to 8250; polymorphonuclear cells 60 to 84; nonfilamented cells 7 to 16; lymphocytes 14 to 40.

Following the birth of her 3rd child she subsequently gave birth to 2 more offspring weighing 8 pounds 11 ounces and 6 pounds 1 ounce in 1943 and 1945, respectively. All 5 children were breast fed and all were living and healthy at the time this article was written.

(I am unable to find Hodgkin's disease mentioned in any of our standard textbooks of obstetrics,—a circumstance which is of course understandable in view of the rarity of the complication. Nevertheless, any physician may perchance encounter it sooner or later, and if so, he will naturally want to know the experience of others in order that he may manage his own case more wisely. The above review of the literature together with the case report is a concise survey of a rather extensive experience and brings out several important points:

1. Hodgkin's disease is rarely aggravated by pregnancy; hence, there is seldom an indication for therapeutic abortion. 2. X-ray therapy and other forms of therapy used in Hodgkin's disease exert no untoward effect on pregnancy. 3. Although 2 or 3 cases have been reported in which the infants manifested the disease, this appears to be most unusual and the great majority have been unaffected.—Ed.)

A CASE OF UTERINE SARCOMA DURING PREGNANCY

I. M. STUTZER

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Genital tumors, especially malignant growths, are seldom observed in pregnant women. Hence the following report of a case of sarcoma of the uterus is of particular interest.

The case was that of a woman 24 years old who had suffered from irregular and rather profuse menstruation from the age of 15. This condition led to a curettage in 1940, followed by a weak menstrual flow which finally stopped altogether. In May, 1944, she went to a gynecologist who discovered a genital hypoplasia. The corpus uteri was small and the ovaries could not be felt by palpation. After treatment with hormones menstruation was resumed but was scanty. In March, 1945, it ceased, and at the end of May the patient suffered a severe hemorrhage, and went to her physician who found an enlargement of the uterus corresponding to a pregnancy of four months. As the menses had stopped two months previously the physician diagnosed a two months' pregnancy in a myomatous uterus. Abortion seemed inevitable and on May 31st the physician removed a fetus of 8 weeks' growth. A probe of the uterus revealed the fact that the cavity was only 10 cm. long and was deflected to the left by a swelling at the base.

Six weeks later the hemorrhages recurred and an examination revealed an enlarged and apparently myomatous uterus. On July 7th a supravaginal removal of the uterus was performed. The tumor within the uterus felt somewhat softer than a myoma and when opened displayed all the characteristics of a malignant neoplasm, the cavity being almost filled with polypoid growths.

Specimens sent to the Pathological Institute of the University of Göttingen for microscopic analysis revealed the following histological picture. The mucous membrane of the uterus had been replaced by a much thicker structure containing only a few mucous glands. This growth was delimited in general by the myometrium although here and there it radiated into the muscle. There were no large blood vessels in the neoplastic tissue, only thin-walled capillaries being seen.

The growth consisted of a many-celled tissue, containing a few fusiform fibers, frequently displaying a transition to a round cell form. Here and there in the tissue showed an inflammatory infiltration, particularly marked in the marginal region between the growth and the muscular wall of the uterus. The intact corpus glands were widely scattered and were in no wise atypical. The structure of the tissue was irregular. All histological indications pointed to the existence of a sarcoma of the corpus uteri.

It might be assumed that the sarcoma was formed after the abortion, but as the operating gynecologist found a tumor in the uterus when the fetus was removed, believing it to be a myoma, it seems almost certain that the sarcoma was formed during pregnancy.

On August 8, 1945, the patient was admitted to the hospital at Göttingen for postoperative x-ray treatment. A gynecological examination showed that the small stump of the cervix was adherent to a compact parametric infiltration which involved the anterior parametrium and a portion of the left parametrium. The right sacrouterine ligament was only slightly infiltered. Following intravaginal and abdominal x-ray treatment the parametric condition disappeared rapidly. When she was discharged from the hospital on September 28, 1945, both parametria, although still somewhat tense, were no longer infiltrated.

Four weeks later her attending physician observed a change for the worse. She was suffering from severe pains in the back and abdomen. A general metastasis had begun. In the abdominal wall between the navel and the right crest of the ilium there were 8 lumps ranging in size from that of a plum to that of a hazel nut. The left parametrium was once more infiltrated to the pelvic wall. Death took place on November 11th, 6 months after the removal of the uterus.

Before citing the known cases of sarcoma of the uterus during pregnancy the author emphasizes the fact that sarcomas of the corpus uteri are more frequent than sarcomas of the cervix. However, sarcomas of the mucous membrane are seldom found among the former. They are mostly sarcomas of the uterine wall.

The cases in the literature cited, 8 in number, were all sarcomas of the mucous membrane of the uterus, but with the exception of the case described by the author, all were located in the cervix. While admitting that the morphological findings of various authorities are not always unanimous, he states that pregnancy seldom takes place when a sarcoma exists in the mucous membrane of the corpus uteri. If the sarcoma of the corpus uteri is not in the mucous membrane, it is more likely to develop during pregnancy as in this case and the embryo may grow undisturbed for some time.

Upon consulting the records of the Women's Clinic at the University of Göttingen, the author found 23 cases of combination of carcinoma of the cervix and pregnancy, but in all medical history he was able to find only 3 authentic cases of carcinoma of the corpus uteri during pregnancy. This he concludes is due to the fact that the ovum may lodge in a carcinomatous uterine mucous membrane, but it finds such poor nutritive conditions that it dies unnoticed in a very short time, and the same is true of sarcoma of the corpus uteri.

(As the author indicates, endometrial sarcoma in association with pregnancy is the rarest of the rare and, as far as I can ascertain, the above case is only the third on record. In a report by Hesseltine on this subject (Jour. State Univ. Iowa, 20: 560, 1930), he refers to a case published by Freund in the German literature and that was apparently the first to be recorded (Deut. Med. Wchnschr., 53: 729, 1927). In Freund's case the diagnosis was made 5 weeks after delivery, the patient having developed fever some time after the first postpartum week. The slightly enlarged uterus had 11 separate areas of sarcoma with one area extending through the uterine wall.

Likewise, in Hesseltine's case, the endometrial sarcoma made itself manifest by a febrile postpartum course. His patient was a 38 year old multipara who suddenly developed high fever 15 days after a normal, spontaneous delivery. The uterus was well above the brim of the pelvis. Even with the treatment for uterine infection the intermittent fever continued daily and when the uterus had become the size of a 4 or 5 lunar months' pregnancy, dilatation and curettage produced a few blood clots, and an abundant "pinkish friable tissue"; considerable purulent material was also released. The temperature fell at once, remained normal thereafter and the uterus decreased rapidly in size. Microscopic examination of the tissue revealed a typical mucosal-cell sarcoma with definite evidence of invasion and extension. Extirpation of the entire uterus, both tubes and ovaries was followed by deep x-ray therapy. The specimen revealed a relatively early malignancy without extrauterine extension as noted in the following excerpt from the pathologist's report: "The mucosa seems to have been entirely replaced by a dull opaque yellowish tissue. This merges indefinitely into the muscularis." Microscopic appearance again confirmed the diagnosis of mucosal-cell sarcoma. At the time of the above report, some 10 months later, no evidence of metastases or recurrence could be elicited.—Ed.)

CHOREA GRAVIDARUM

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Causes suggested for chorea gravidarum include heredity; toxemia, based on the fact that chorea manifests itself after the fourth month when the placenta is fully developed, and that interruption of the pregnancy results in disappearance of the chorea syndrome; infection, on the basis of similarity to Syndenham's chorea, and the high incidence of cardiac disease and histories of previous chorea or rheumatism in these cases; the "infantilism theory," that it is a deficiency of the entire endocrine system; allergy; syphilis; and mental disturbance.

The incidence is rare. Only a few cases of childhood chorea recur during pregnancy. The disease occurs most frequently in young women pregnant for the first time, and may or may not recur in subsequent pregnancies.

Chorea is more serious for pregnant women than for any other group, the mortality reports varying from 6 to 36 per cent. The prognosis is worse for those without a previous history of chorea in childhood. Complications are due to muscular spasms of the throat, tongue and larynx, and include exhaustion, aspiration pneumonia, cardiac decompensation, and psychosis.

Though about half the pregnancies go to term, the fetal mortality is 50–70 per cent. Many of the children born alive are defective, possibly as a result of toxic interferences with development. "The chief danger to the child as far as heredity is concerned is an increased susceptibility to rheumatism which in turn may cause chorea."

The symptoms of chorea gravidarum are choreiform movements, mild or severe, which disturb the patient's rest and lead to exhaustion.

Prophylaxis consists of proper prenatal care: proper diet, rest, isolation, proper elimination, exercise without fatigue, freedom from worry, removal of all foci of infection, special attention to neurotic patients, and proper vitamins.

According to Bumm, the mild cases develop slowly and clear up on diet and psychological treatment with or without sedation. One-third of his cases had an acute onset with rapid dissemination to the muscle groups and the onset of psychosis, with delirium, high temperature, and general severe toxemia termination in death; in this group rapid therapeutic abortion is advocated. Royston believed the uterus should be emptied as soon as chorea is definitely diagnosed, DeLee and Greenhill would empty the uterus if the condition became progressively worse. They recommend that at or near term a cesarean section should be performed in primiparas, though in most in tances simple induction of labor may be preferable. Dutra treated 2 cases with pyridoxine hydrochloride (B_6) with good results.

A case report is presented of a 17-year-old primipara with no previous history of rheumatism or chorea, in whom chorea gravidarum appeared in the second trimester of pregnancy. On admission she was undernourished, with poor hemic

component, typical choreiform movements, and a soft systolic murmur which was not heard on later consultation. An EKG later indicated mild ventricular myocardial disease.

Therapy consisted of isolation, rest, sedation (with ammonium bromide, phenobarbital, chloral hydrate), intravenous magnesium sulfate, calcium, vitamins, pyridoxine, liver and iron and blood transfusions.

Five weeks after admission patient went into labor. After no progress in dilatation of the cervix, a single flap cesarean section was done with intravenous sodium pentothal anesthesia. The premature male infant lived for only a few days; autopsy revealed local hemorrhages and serous effusion. The mother's recovery was uneventful, and choreiform movements markedly decreased.

This case may belong to those in which toxemia, avitaminosis and poor nutrition were etiological factors. It emphasizes the prophylactic value of proper prenatal care. In the severe cases death would follow interruption of pregnancy; surgery would be more serious than induction of labor. The use of therapeutic abortion should not be considered in the mild cases.

STATUS EPILEPTICUS COMPLICATING PREGNANCY

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Status epilepticus in pregnancy is uncommon, the few cases reported mostly fatal. The effect of pregnancy on idiopathic epilepsy is variable. Status epilepticus may occur at any time in pregnancy, labor, or puerperium, even as the first sign of epilepsy, though often preceded by more violent and more frequent fits despite adequate therapy. A fatal termination is almost the rule, although occasional patients recover, and emptying the uterus offers a very slender chance.

Burnett (1946), in an excellent survey of the literature, reports a case which recovered after induction of labor by low rupture of the membranes under thiopentone anesthesia in the thirty-third week of pregnancy. Although the living child was not born for a further 5 days, complete recovery resulted, and 2 months later the patient was having fits at her normal frequency.

Sterilization has been advised for any patient who has suffered from status epilepticus in pregnancy, since chances of recovery seem negligible should the situation recur.

A case is reported here of a 23-year-old woman, 3 months pregnant with her first child, married 3 days before admission to the father of her child. She was admitted to the Royal Infirmary December 29, 1946, in status epilepticus. At 21 she began to have major epileptic fits, finally diagnosed idiopathic epilepsy. There was no family history of convulsions. Her occasional fits were controlled with phenobarbital, but after 1 year she ceased to take the drug, with the result that she went into status epilepticus for a few hours 18 months before the present admission. Pregnancy so far had been uneventful and free from fits, without phenobarbital.

Examination showed a well-developed young woman, comatose, with stertorous respiration and slight cyanosis, pulse 120 and of good volume, blood pressure 130/70. Reflexes were absent, plantar responses extensor, no localizing central nervous system signs. There was no edema, and optic fundi, heart, lungs and abdomen were normal. Vaginal examination revealed pregnancy of about 3 months' duration. Urine contained a trace of albumin, no sugar or acetone. The temperature was 98.8° F. (37.1° C.). She was incontinent of urine and feces, had no urinary retention.

Generalized epileptiform fits of 1–3 minutes followed at intervals of 10-15 minutes, without response to intramuscular sodium phenobarbital, intravenous thiopentone preventing a continuous succession of fits. Oxygen was given continuously.

Sodium phenobarbital, 3 gr. (0.2 g.) was given intramuscularly twice daily, 0.25 g. of thiopentone intravenously as needed. Ten ml. of clear fluid at a pressure of 160 mm. of water was removed in lumbar puncture, producing little relief.

During the first 5 days patient remained comatose, with major fits varying irregularly from 4 to 60 per day. Fluids were given per rectum and by transnasal tube. There were no other physical signs, and no evidence of increased intracranial pressure. Lumbar puncture on the 30th was normal, on the 31st contained 30 red cells per c. mm. Temperature and pulse rose on the 31st.

The next day patient developed a pneumonia, evidenced by sputum containing Staphylococcus aureus and pneumococci, which was treated by penicillin, sulfameza'hine, and by paraldehyde per rectum or gastric tube substituted for the barbiturates. Beginning January 3 there were no further fits, and by January 6 patient was fully conscious and symptom-free. On the 9th paraldehyde was discontinued; phenobarbital was given by mouth, 1 gr. (65 mg.) 3 times a day. X-rays of chest and skull were normal. Penicillin was stopped January 16. The next day patient's physical condition was excellent, but she became tearful and uncooperative, developed clonic leg twitchings in the presence of any audience, and said she could not walk. Hysteria was diagnosed. On January 20 patient was discharged under observation, physically normal, pregnancy undisturbed, but grossly hysterical, on phenobarbital 1 gr. 3 times a day.

By June the patient was feeling well, with no hysterical signs and no fits, and taking her medication. On July 21, a normal female child (3.7 kg.) was delivered spontaneously at term; there were no fits during labor, and both mother and child progressed satisfactorily.

The differences between this case and Burnett's suggest that the prognosis may be better when omission of specific therapy is a factor than when status epilepticus appears in pregnancy despite previous adequate therapy. Though omission of medication may have been responsible here, pregnancy, probably through the changes in hormonal balance and intracellular fluid retention which may lead to a slight cerebral edema, may have exerted an additional influence, since this attack was much more severe than the earlier one. Possibly the onset earlier in pregnancy may also indicate better chance of recovery.

PATHOLOGY OF LABOR AND PUERPERIUM

POSTPARTUM HEMORRHAGE AND SHOCK

Robert D. Mussey

The principal causes of postpartum hemorrhage are uterine inertia, extensive laceration of the birth canal, and retention of all or part of the placenta in the uterus; less common are conditions such as uteroplacental apoplexy (couvellaire uterus), rupture of the uterus, vulvar varicosities and inversion of the uterus.

Uterine inertia may be due to poor uterine musculature, prolonged labor or overdistention of the uterus, uterine tumors, analgesia and anesthesia. In the course of prolonged labor the patient's strength should be maintained by rest and fluids, and analgesics and anesthesia should be used in moderation.

Lacerations of the birth canal may occur in carefully conducted labor, but too frequently result from efforts to deliver the baby through an incompletely dilated cervix, manual dilatation, and faulty use of forceps.

Mismanagement of the third stage of labor usually can be avoided if the uterus is left alone during placental separation, which normally occurs within 5–10 minutes following delivery of the baby. The body of the uterus, at first globular, becomes soft and flattened as it relaxes, during which time separation occurs. As separation nears completion, the uterus contracts again, becomes globular and rises to or above the level of the umbilicus. At about this time the placenta is expelled to the vagina. If the placenta is still in the uterus, pressure applied above the pubes causes the uterus to rise and the cord is drawn slightly into the introitus; if the placenta is in the vagina, under such pressure the cord remains stationary or descends slightly. If the fundus is handled too much or squeezed, the placenta becomes only partly detached and bleeding occurs until the placenta is expelled or extracted.

Retention of part or all of the placenta, or uterine fibromyomas, may prevent the uterus from contracting properly and thus result in bleeding. Bleeding from the site of placenta previa is difficult to control because it is too low for compression by the contracting uterus. In placenta previa any manipulation which would cause laceration of the cervix must be avoided.

When the placental site is the source, the blood flows profusely. Bleeding from lacerations is usually less profuse but more constant, and brighter in color. Bleeding may be delayed, as when blood collects and clots in the relaxed uterus and is expelled when the uterus contracts. A ruptured uterus may bleed undetected, unless there is alertness for signs of internal hemorrhage. Close observation of the patient directly after delivery and for at least the next hour is most strongly emphasized. Hemorrhage may not at first bring evidence of shock

(paleness, sweating, rapid pulse, etc.), but if it continues close observation and repeated pulse and blood pressure checks are essential because of the insidious onset of shock. Systolic decrease from more than 100 mm. mercury to 80 mm. or less, especially with a low pulse pressure, indicates the patient is nearing or in shock.

Adequate prenatal care, including examination of the blood, treatment of anemia if present, correction of nutritional deficiencies, early recognition and treatment of toxemia, and pelvic mensuration, plays a leading role in reducing the incidence and severity of postpartum hemorrhage. Careful management of labor is also important: in protracted labor, sedatives and intravenous glucose to prevent or relieve exhaustion; avoidance of excessive analgesia and anesthesia; close observation of the fundus from the delivery of the baby to separation of the placenta, inspection of the placenta, oxytocic drugs; the patient put to bed and the fundus observed frequently and kept under control for at least an hour.

In management of hemorrhage, the first consideration is to control the bleeding, the second to replace lost fluid, and the third to treat the shock and anemia.

If bleeding is from retention of the placenta, the placenta must be delivered, sometimes by simple expression or by the Credé maneuver. Manual removal under aseptic technic should be done without delay if first efforts fail, or if placental fragments or an accessory lobe is retained. If the uterus should fail to contract firmly following delivery of the placenta and an oxytocic given hypodermically, vigorous massage is used, with one hand on the abdomen and two fingers of the other in the vagina if necessary. More rapid and prolonged action from a suitable oxytocic is obtained by intravenous administration. Usually hemorrhage is controlled if uterine contraction is maintained. If not, the birth canal should be inspected immediately; if the bleeding is due to lacerations, they should be repaired at once.

Should bleeding continue to be excessive, it is advisable at once to pack the uterus firmly with sterile gauze, especially when the uterus tends to relax. Two fingers are inserted into the uterus with the palm of the hand placed anteriorly. The gauze is carried along the fingers into the uterus with packing forceps or placental forceps. Washed iodoform gauze 2 inches wide in 5 yard lengths is employed, several lengths tied together when needed. In placenta previa uterine and vaginal packs are a routine precaution. (The iodoform gauze appears to inhibit the growth of organisms. Only one sensitivity to iodine, a slight skin erythema, has been found in 30 years of use.)

Hysterectomy has occasionally been lifesaving in certain massive hemorrhages, and is imperative in uterine rupture.

Some method should be used to estimate blood loss, and the parturient should be given as much fluid intravenously as she has lost (beyond the normal amount of less than 300 c.c.). Normal saline solution, except in toxemia, or 5 per cent glucose should be started immediately when intravenous fluid is indicated, and quickly supplemented by blood or plasma. If whole blood is used, care must be taken to avoid incompatibility. Six per cent solution of acacia is sometimes used, though it is not absorbed quickly from the blood, or 6 per cent solution of

specially prepared gelatin, to maintain blood volume and pressure till suitable whole blood is available.

In urgent need, transfusions are begun during the procedures employed to stop the bleeding. Operative measures should be begun only after shock is under control. Sometimes vasoconstricting agents, such as 3 minims of epinephrine, given intravenously with blood or other solutions help in initial treatment of shock. At least 500 c.c. of fluid, to meet the needs of the heart, must be given with epinephrine. It may sometimes be advisable to give fluids into more than one vein simultaneously, or under positive pressure when blood pressure is extremely low.

PROLONGED LABOR, WITH SPECIAL REFERENCE TO POSTPARTUM HEMORRHAGE

ALEXANDER M. WATSON

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The causes of prolonged labor can be divided into two classes:

1. Those variations in shape and size of the pelvis that obstruct passage, and anomalies of the fetus itself; cases of faulty presentations; such conditions as tumors or cysts in the pelvis, bicornute uterus and a long rigid cervix.

The majority of these causes may be detected by complete and careful prenatal examinations, including x-ray examination late in pregnancy to determine pelvic measurements and fetal size and shape. They will not be discussed here.

2. Inertia uteri, which may develop during labor and continue into the postpartum period, may appear without warning, and in the postpartum period may cause hemorrhage.

Secondary inertia is a temporary uterine exhaustion usually appearing in the second stage of labor, resulting from an obstruction which is not insuperable. Primary inertia uteri has been defined as a complication of labor characterized by uterine contractions which from their onset are sluggish, infrequent, and incoordinate. It is a common type of dystocia, resulting rather from the inadequate contraction of the uterus than from the rigid cervix.

The cause of primary inertia is not known, although disturbances of one or more of the theoretical causes of normal labor, such as increased venosity of placental blood, mechanical distention of the uterus, senility of the placenta, maturity of the fetus, or influence of hormones, have been suggested. Primary inertia is known to occur more frequently in elderly primiparae and in multigravidae who are emotionally unstable and apprehensive. "One thing which all patients with inertia uteri have in common is a nervous condition of apprehension and a feeling

that it is impossible for them to deliver their babies." These anxious patients can usually be detected during prenatal care, and everything possible must be done then to gain their confidence and build their morale. Douglas P. Murphy of the University of Pennsylvania has done some interesting work with the tocograph, for measuring uterine motility, in prenatal forecasting of the possible primary inertias; his book published this year lists his observations and conclusions.

Nalle has suggested an underlying disturbance of the autonomic system, calcium deficiency, or a combination of the two. In line with Nalle's theory and his use of calcium gluconate with vitamin D from the third month, the author has found calcium gluconate grs. 30 daily for the last trimester, with vitamin D, of great benefit.

In primary inertia in labor, the pains are irregular and cause great discomfort. No progress is made; the fetal parts do not engage and the os does not dilate, though prenatal examinations have shown there are no abnormalities of position, pelvis or fetus that would obstruct labor.

Treatment during labor consists in trying to establish normal labor. There should be long rest periods of several hours with the use of sedatives, preferably demerol, 100 mg. with hyoscin hydrobromide gr. 1/100, repeated in an hour or 2 if needed. In many cases, labor then becomes normal and progresses favorably.

The oxytocic drugs should not be used unless the cervix is fully dilated and it is certain there is no mechanical obstacle to the delivery of the child. The alkaloid ergonovine or ergotrate (ergometrine) is used almost entirely postpartum. Pituitary extract will often cause normal strong contractions that will terminate the labor, in the presence of primary inertia, and is very useful under certain regulations. It should not be used (1) if the intrauterine tension is high or if the uterus is in a state of tetanic contraction, (2) if the os is not fully dilated or easily dilatable, (3) if there is any obstruction to labor, such as deformed pelvis or fetal anomaly. Lastly, the dose should be small, about 2 minims, of obstetrical pituitrin.

In many cases of primary inertia some form of obstetrical operation may be needed, such as forceps at midpelvis or outlet. Use of high forceps is dangerous; podalic version is preferable. Due to long labor and probable examinations and loss of the liquor amnii, cesarean section is contraindicated because of the great danger of sepsis.

The most serious complication is postpartum hemorrhage, a direct result of ineffectual uterine contractions extending into the postpartum period. Odell, Randall and Scott found the incidence of postpartum hemorrhage higher in mothers who had operative interference of any sort to conclude the labor than in those who delivered spontaneously. In such instances they give early a 5 minim dose of pituitary extract followed by ergotrate. If this is not successful, they advocate douching the uterus with cold sterile water and tamponade.

If hemorrhage develops after the delivery of the placenta, the uterus should be grasped firmly and massaged to induce contractions. Five minims of pituitary extract is given intramuscularly, followed by ergotrate 1/320 by the same

method. If the bleeding continues, the vagina and cervix are examined for lacerations, which should be sutured. If the bleeding is from the uterus, any secundines present there should be removed manually. In case the patient is still bleeding, it will be necessary to pack the uterus. At this stage plasma is given and arrangements are made for compatible blood transfusion. Packing the uterus may be lifesaving. Infection is not very likely to occur in a modern hospital, and usually can be controlled by penicillin, sulfonamides, and blood transfusions.

In postpartum hemorrhage before the delivery of the placenta, the placenta should first be delivered, by Credé method of expulsion or if it fails, by manual separation. Pastore has stated that the placenta should be separated by the ulnar side of the hand, starting at the top of the fundus and separating downward, so the uterus contracts on the retreating hand and avoids the bleeding of the reverse method. He further says that if in inertia the placenta has separated but is not expressed, clots accumulate and blood loss is great. When the uterus changes from a discoid to a globular shape, the placenta has separated. The rise of the fundus in the abdomen is the sign of the descent of the placenta rather than of a separation, and indicates the accumulation of clots. No repairs should be attempted until the placenta is expressed. Efforts to express the placenta by pressing the uterus down into the pelvis and causing pressure on the uterine veins increase the bleeding. The assistant should "grasp the fundus in his right hand with the fingers behind and the thumb in front of the fundus. The uterus is then gently massaged, but there should be no downward pressure. The left hand of the assistant is then placed flat on the abdomen just at the symphysis and pressure is exerted with the right hand while the left hand prevents the uterus from entering the pelvis. As the placenta passes through the cervix, the uterus is lifted up as far as the umbilicus. With this method, there is no danger of inversion of the uterus."

FACE PRESENTATION

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From January 1, 1931 through July 31, 1946, at the Philadelphia Lying-In Hospital, there were 61 face presentations, an incidence of 1 in every 576 deliveries. The purpose of this paper is an analysis of these 61 cases as to etiology, management and end results.

There were almost an equal number of primiparous and multiparous patients; but almost 60 per cent of the multiparous patients, or 30 per cent of the total patients, had had two or more children. Of the primiparous patients, there were 11, or 38 per cent, with some form of pelvic abnormality, while of the 32 multi-

that it is impossible for them to deliver their babies." These anxious patients can usually be detected during prenatal care, and everything possible must be done then to gain their confidence and build their morale. Douglas P. Murphy of the University of Pennsylvania has done some interesting work with the toco-graph, for measuring uterine motility, in prenatal forecasting of the possible primary inertias; his book published this year lists his observations and con-clusions.

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over one-half of the cases requiring major operative procedure for delivery were managed by version. Eleven of the versions were done between 1931 and 1938, inclusive, while only three have been done since 1938. On the other hand, between 1931 and 1938 only eight patients, or 25 per cent, delivered spontaneously, while since 1938 there were eleven, or almost 40 per cent, delivered spontaneously. This parallels the trend of this clinic to do fewer versions.

NONFATAL PULMONARY EMBOLISM BY AMNIOTIC FLUID CONTENTS WITH REPORT OF A POSSIBLE CASE

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To date no case report can be found in which the *clinical* diagnosis of amniotic fluid pulmonary embolism had been made either preceding or following the death of the patient; in all instances it seems to have been an unexpected finding at necropsy. Furthermore, the authors have been unable to find a single recorded instance of recovery of a patient suspected to have had this type of embolus.

The authors present the case of an 18-year-old primigravida, who suddenly went into profound shock, developed acute pulmonary edema with cyanosis, and was in imminent danger of death immediately following the delivery of a living 6 pound 3 ounce frank breech. Because of rise in blood pressure, sudden gain in weight, three weeks postmaturity, engagement of the presenting part at the spines, and favorable cervix, admission for induction had been advised. She was admitted at 8:15 a.m., Jan 29, 1947, not in labor, with a blood pressure of 140/80. A routine medical induction with 1 ounce castor oil, a soapsuds enema, and pitocin was given. Uterine contractions became regular at 1:00 p.m., occurring every five to seven minutes. Labor progressed slowly although contractions were good, and 50 mg. of demerol and grain 1/150 of scopolamine intravenously were given at 6:30 p.m. Scopolamine 1/150 grain intramuscularly, was repeated at 7:30 p.m. At 4:30 p.m. blood pressure was 190/100 and at 5:30 p.m. 160/100.

At 7:30 p.m. the cervix was fully dilated, fetus was presenting as a frank breech in right sacroposterior position. First stage lasted eight hours and thirty minutes.

She continued in the second stage of labor for two hours, when the breech reached the perineum and the membranes were artificially ruptured. The contents of the amniotic sac consisted entirely of undiluted meconium.

Nitrous oxide and oxygen anesthesia was started at 9:55 p.m., and the anesthetist noted that adequate anesthesia could be maintained with a minimal amount of nitrous oxide, so that at times the patient received practically pure oxygen. In spite of this, moderate cyanosis was noted by the anesthetist periodically throughout the delivery and repair.

parous patients there were only seven, or 22 per cent, showing pelvic abnormality. One-half of the patients with abnormal pelves gave birth to infants weighing 7 to 8 pounds. Almost 25 per cent of the infants were well above average birth weight i.e., 8 pounds or more. Therefore, instead of only 18 cases of disproportion (i.e., taking pelvic measurements alone as the criterion), there were 30 cases in all with some degree of cephalopelvic disproportion; or, almost one-half of the cases showed either small pelvis by measurement or an average pelvis with an oversized infant. The incidence of monstrosities in this series was high. Of the 61 infants, seven, or over 11 per cent, were monstrosities. Five of these infants were anencephalic monsters, while the other two were acraniorachischisis. This figure is somewhat lower than the average given in most texts for the incidence of monstrosities in face presentation.

Morbidity and Mortality. There were no maternal deaths in this series, and the maternal morbidity (using the standard of morbidity as a temperature of 100.4° F. occurring during any two 24-hour periods through the tenth day excluding the first twenty-four hours) was 8.7 per cent. The fetal mortality for face presentation was nearly four times the average fetal mortality for the hospital, but compares favorably with most statistics for face presentation. A total of twelve, or 19.7 per cent, of the babies were either stillborn or died before the tenth day. There were eight, or over 13 per cent, stillbirths and four, or 6.5 per cent, neonatal deaths. This is an uncorrected fetal mortality; of these twelve infant deaths, seven were monstrosities and one was a normal infant weighing less than two pounds.

Type of Delivery. Ninteen, or almost one-third, of the patients delivered spontaneously, including two primiparous patients and three multiparous patients with posterior positions, all of which rotated spontaneously. Another 25 per cent of the patients were delivered by forceps without forceps rotation. So there was a total of six posterior and four transverse positions which rotated spontaneously (one transverse was rotated manually and then delivered by low forceps). Internal podalic version and breech extraction was used in almost 25 per cent of the cases; cesarean section was the method of delivery in eight, or 13 per cent of the cases. Two of the sections were done electively before the onset of labor, one with placenta previa as the indication and the other after X-ray diagnosis of face presentation was made.

According to this small series the prognosis for both the mother and the infant does not seem grave. Although the maternal mortality for the hospital is generally low, the absence of a maternal mortality in this series cannot be disregarded. At first glance an infant mortality of 19.8 per cent seems high; but a corrected figure (excluding monsters and infants under 3 pounds birth weight) of four, or 6.5 per cent, compares favorably with the general average for the hospital for the years included in this series.

There has been a definite trend in this hospital toward more conservatism in the treatment of face presentation. The fact that over 50 per cent of the cases delivered spontaneously or with only low forceps supports the dictum, "If a 'face' is progressing, leave it alone". Fourteen, or almost 25 per cent, of the cases were managed by internal podalic version and breech extraction. This means that

Chest x-ray on the 5th postpartum showed that the extensive areas of infiltration in both lung fields had completely cleared.

The diagnosis of pulmonary embolic phenomena from particulate matter in amniotic fluid is suggested as the etiologic factor for the symptom complex which developed. The authors cannot didactically state that this is positively a case of amniotic particulate embolism, as there are no known means of making a positive clinical diagnosis in the living patient. However, they believe it presents the most likely explanation for the symptom complex that occurred.

The recovery of their patient may be explained by a series of fortuitous events: (a) early diagnosis and appropriate therapy; (b) excellent physical condition of the patient; (c) the fact that she was under a general anesthetic during the embolizing episode; (d) the apparent rapid "absorption" or at least complete removal of the particulate matter from the lung fields as shown by x-ray. The case is presented to call attention to the possibility of recognizing this syndrome soon after its occurrence in order that proper therapy be started immediately to prevent a fatal termination.

(This dramatic case was presented at a meeting of the Baltimore Obstetrical and Gynecological Society and was discussed at length, with opinion about evenly divided as to whether it was or was not a true case of amniotic fluid embolism. For my own part I find it difficult to understand the x-ray findings and it is upon these, of course, that the diagnosis in this case chiefly rests. Although I have not reviewed all the protocols of reported cases in detail, it is my recollection that the lungs at autopsy in amniotic fluid embolism are usually entirely normal to gross inspection and that the characteristic findings, that is plugged terminal arterioles, are demonstrable only on microscopic section. Large infarcts, such as suggested in this case by the x-ray film, have never been reported as far as I know.

This whole question was reviewed in extenso in a long editorial note in the February, 1948 issue of the Survey, pp. 35–37. Here emphasis was placed on the fact that pulmonary fluid embolism is believed to bring about an anaphylactoid reaction because of the extremely small size of the particles dispersed through the lungs and that the mechanism is quite different from thrombotic pulmonary embolism. The x-ray findings in the above case suggest a large embolus rather than embolism from particulate matter. However, we know so little about this whole phenomenon that one person's guess is about as good as another's and my skepticism may be ill-founded. In any event the authors are cautious to report their experience as a "possible case" only.—Ed.)

ANTICOAGULATION THERAPY WITH HEPARIN PITKIN MENSTRUUM IN THROMBO-EMBOLIC DISEASE COMPLICATING THE PUERPERIUM AND GYNECOLOGIC SURGERY

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During the past three years or more, 251 patients with venous thrombo-embolic disease received subcutaneous heparin in the Pitkin menstruum with gratifying results. Fifty-three of these 251 subjects were obstetric or gynecologic patients.

Delivery was preceded by a deep left mediolateral episiotomy. Strong supra-fundic pressure was made by the assistant (W.S.) until the operator (L.M.S.) could reach the anterior groin with an index finger. By moderate traction the breech was delivered without great difficulty. The body, arms, and shoulders followed in the usual manner. Piper forceps were applied to the aftercoming head to complete the delivery. The 6 pound 3 ounce male child was born at 10:10 p.m. Jan. 29, 1947. The second stage of labor lasted two hours and forty minutes. Ergotrate, 1 ampule, was given intravenously at 10:10 p.m., and 1 ampule of pitocin intravenously at 10:16 p.m. The placenta and membranes were expressed intact at 10:12 p.m., and it was noted that the membranes and amniotic surface of the placenta were stained a deep meconium green. The third stage lasted two minutes. Total labor eleven hours twelve minutes. Blood loss was estimated to be 150 cubic centimeters.

The baby appeared to be in good condition, but initial respiration and crying were slightly delayed—being two minutes fifty seconds, and four minutes thirty seconds, respectively.

Toward the end of the episiotomy repair it was noted that the blood oozing from the perineum was quite dark, and further inspection revealed mixed pallor and cyanosis of the face, and marked cyanosis of the fingernails. The pulse was found to be hardly obtainable, rapid and thready. Blood pressure could not be obtained. Respirations were rapid, shallow, and labored. Immediate auscultation of the chest revealed both lung fields to be filled from apices to bases with coarse, moist, bubbling râles, so loud as to almost obscure the very rapid heart sounds. This occurred at 10:30 p.m., eighteen minutes post delivery.

Anesthesia was immediately stopped, 100 per cent oxygen given, patient's position changed to reverse Trendelenburg, and cardiac stimulants were ordered. Medications given were 1 ampule of digalin intramuscularly at 10:40 p.m.; 1 ampule of adrenalin intramuscularly at 10:42 p.m., 1/150 grain of atropine intravenously at 10:45 p.m. The patient was still deeply cyanotic, both skin and nails, dyspneic in spite of constant oxygen and respirations were rapid and shallow. The diagnosis of pulmonary embolus due to meconium was ventured at this time by an attending obstetrician (W.S.) who was present. Intravenous fluids were interdicted for the time being.

Portable chest film showed that the heart did not appear to be enlarged. Mediastinum was not shifted. The intercostal spaces were equal bilaterally. Diaphragms were in normal position. There was an area of increased density involving the second and third anterior interspaces on the left side, and also involving the lower two-thirds of the right lung, more marked at the base of the seventh rib posteriorly. From the shape of these dense areas, infarctions could not be ruled out.

Treatment was intensive and consisted of tourniquets, cedilanic, morphine, oxygen tent, penicillin and blood transfusion given very slowly. The patient's condition remained grave for 24 hours, with intense edema of the lungs and coughing up of frothy, watery, blood tinged sputum. Remarkable improvement began 35 hours postpartum and continued to discharge 15 days postpartum.

keep the patient "heparinized" for approximately two days. Therefore, administer the contents of one 3 cc. ampule every second day throughout the requisite period of heparinization. If the patient receives a blood transfusion during the period of heparinization, administer the contents of one 3 cc. ampule immediately following the transfusion, irrespective of when or how many previous deposits have been given. If, for any reason, there is need to stop the effect of heparinization, this can be accomplished immediately by the intravenous administration of 250 to 500 cc. of whole blood or bank blood not more than 3 days old.

Suggestions for Treatment.—1. In cases of thrombophlebitis, it is advisable to inject the heparin into the thigh which is normal. Avoid using the affected thigh for deposition of heparin until the swelling has partially receded.

2. For hyperreactors employ the 2 cc. ampules which contain 200 mg. of heparin sodium salt. For hyporeactors administer 400 mg. This is accomplished by combining two 2 cc. ampules each containing 200 mg. of heparin sodium salt. Where vasoconstrictors are indicated use only one ampule with vasoconstrictors in the combination inasmuch as the amount of vasoconstrictor drugs contained in the one ampule will suffice for the entire dose of heparin.

3. As a general rule for effective heparinization the blood coagulation time should be not less than 2 to 3 times the control coagulation time, i.e., 30 to 45 minutes as contrasted with a control time of 9 to 15 minutes.

Adjuvant Therapy.—Coincident with the institution of heparin therapy the liberal use of papaverine is recommended, 1 to 3 grains every 4 hours intramuscularly or even intravenously and, later, maintenance dosages by mouth. Smoking is strictly prohibited. Paravertebral block, although used extensively in arterial occlusions, is not used by the authors in thrombophlebitis as a routine measure since they have found that venous spasm disappears promptly following administration of subcutaneous heparin.

While the addition of antibiotics and/or sulfonamides to the treatment program is not discouraged, these are not necessary in the management of the usual type of thrombo-embolism encountered in obstetric and gynecologic practice. Should, however, there be any identifiable infective etiology, the antibiotic and/ or chemotherapeutic program should then be pursued intensively, consistent with the nature of the infective organism. The mere presence of a febrile reaction does not connote bacterial invasion and may well be attributable to the mere presence of intravascular thrombosis particularly when the blood clot engages the vessel wall and precipitates an inflammatory intimal reaction.

In the authors' series the treatment of venous thrombo-embolic disease with subcutaneous heparin in the Pitkin menstruum was attended with lessened morbidity, prompt and rapid clinical improvement, and little or no residual edema. Treatment failures with other methods have subsequently ended in recovery following the routine administration of the heparin/Pitkin menstruum preparation. As a result of observations of its clinical deportment, the subcutaneous administration of heparin in the Pitkin menstruum is recommended as a safe, simple, practical, and effective method for anticoagulation therapy in thrombo-embolic disease complicating the puerperium and gynecologic surgery.

Treatment program

Formulae for Clinical Use. The ampules for clinical use, prepared and distributed by William R. Warner & Co., Inc., New York, are as follows:

Heparin/Pitkin Menstruum (V.C.)

    ampules, 2 cc.—each ampule containing 200 mg. heparin sodium salt with vasoconstrictors.

    ampules, 3 cc.—each ampule containing 300 mg. heparin sodium salt with vasoconstrictors.

Heparin/Pitkin, Menstruum (Plain)

    ampules, 2 cc.—each ampule containing 200 mg. heparin sodium salt; no vasoconstrictors.

    ampules, 3 cc.—each ampule containing 300 mg. heparin sodium salt; no vasoconstrictors.

Dosage Plan. In general, body weight and individual reactivity dictate the amount of heparin/pitkin menstruum to be used in a given case. For the initial injection, body weight may be used as a guide. Patients weighing up to approximately 150 pounds (67.8 Kg.) should be given an initial dose of 300 mg. of heparin sodium salt; patients over this weight should be given an initial dose of 400 mg. Subsequently the dosage should be adjusted according to the intensity of the "heparin effect" as estimated by the coagulation time. Compared with a normal coagulation time of 9 to 15 minutes (Lee-White modification of Howell's method), a coagulation time of 30 to 60 minutes is considered an adequate "heparin effect." In actual practice it will be found that a conventional dose of 300 mg. of heparin will suffice for about 90 per cent of subjects who are normal reactors. The remaining 10 per cent are either hypo- or hyper-reactors, requiring 400 or 200 mg. dosages respectively.

Method of Administration. 1. Warm the ampule gently by either holding it under running hot tap water, or immersing in a container of hot tap water until the contents become fluid.

  2. Shake thoroughly to disperse any precipitated material.

  3. Draw the contents of the ampule into a dry, sterile 5 c.c. or 10 c.c. syringe, using a sterile needle, gauge 18 (2 inch length). After the contents have been drawn up, the 18-gauge needle should be replaced by a 20-gauge needle for the actual injection.

  4. Inject the contents immediately into the deep subcutaneous (or superficial intramuscular) tissue, preferably in the anterior or lateral aspect of the thigh. When subsequent injections are required, use the right and left thigh alternately and avoid sites of previous injection. Do not inject into sites where pressure may be exerted upon the injected area.

  5. Be certain that the contents of the syringe are not too hot prior to the injection. The syringe and contents should feel only slightly warm.

  6. *Do not apply* either heat or cold to areas of deposition unless for purposes of accelerating or retarding release of the drug.

Clinical Use.—In the average case use the entire contents of one 3 c.c. ampule containing 300 mg. of heparin sodium salt. This dose should be sufficient to

THE NEWBORN

CEREBRAL DAMAGE IN INFANTS AND IN CHILDREN

SOME OBSERVATIONS ON ITS CAUSES AND THE POSSIBILITIES OF ITS
PREVENTION

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San Francisco

(Presidential Address, American Pediatric Society)

Amer. J. Dis. Child., 74: 1–9, (July) 1947

In the present study there are 99 cases of cerebral atrophy proved by air encephalograms, in all of which the procedure was carried out because of known mental deficiency, spastic paralysis, convulsive state, a combination of these, or, in 4 cases, other neurologic defects. Mental deficiency was present in 74 per cent, spastic paralysis in 43 per cent, and the convulsive state in 48 per cent. As thorough a history as possible was taken in each case, and the probable factors contributory to cerebral injury grouped according to the period—prenatal, paranatal or postnatal—in which they occurred. Such episodes occurred during more than 1 period in 26 instances. The paranatal period shows only slightly higher incidence than the prenatal, and the postnatal period is represented in a quarter of the cases.

In the prenatal period placental separation is by far the most frequent, occurring at least as a contributory factor in about 20 per cent of the total cases, causing impairment of the oxygen supply and doubtless other bloodborne necessities to the fetus. The severity and promptness of injurious effects on the fetal brain in such circumstances are shown in Clifford's study of placenta previa. Toxemia of pregnancy is also a conspicuous factor; here massive infarction of the placenta sufficient to cause fetal death has been observed, as well as placental separation. A special hazard to the very large infant during labor is suggested by the number (9 per cent of the series) weighing 3800 gm. or more at birth. In 2 cases there was heart disease with evidence of decompensation, the effect on the fetus presumably being a stagnant anoxia, from slowing of the uterine circulation. In pneumonia, as in cardiac decompensation and in others not represented here, where the oxygen supply is reduced, the effect on the fetus may be much greater than on the mother, since the fetus lives under reduced oxygen tension, maintaining a fuller utilization of available oxygen but a smaller margin of safety. Even a slight reduction below the margin of safety for hours or days results in anoxic damage, to which the cortex is most susceptible. In rubella, the virus apparently damages the nervous and other fetal tissues, if maternal infection occurs during the first 2 months of gestation.

A CASE OF PUERPERAL SEPTICAEMIA DUE TO FUSIFORMIS NECROPHORUS

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Little emphasis has been placed on the occurrence of puerperal infections due to the Fusiformis group of organisms, though members of this group are not infrequently pathogenic. The organism has been found in puerperal infections, and also in the normal uterus, vagina, and mouth, and in carious teeth and lung abscesses.

A case is reported of a woman, para-2, admitted in 37th week of pregnancy because of repeated small vaginal hemorrhages, with a diagnosis of marginal placenta previa. A few hours after admission the membranes ruptured and the baby was born spontaneously, without assistance, 10 minutes later. Placenta and membranes were expelled intact. Fever (101.2° F.) was present the next evening. Sulfamezathine had no apparent effect. A week later temperature was 104° F. and patient was suffering from rigors. There were no other special symptoms. After exclusion of urinary infection, an anaerobic streptococcal infection seemed likely. Penicillin was given, 100,000 units followed by 50,000 units every 3 hours for 48 hours. Fever had then abated. Patient felt well but resented the needle. Penicillin 100,000 units morning and evening was continued for 4½ days. Recovery was uneventful.

Aerobic blood cultures were sterile, but anaerobic cultures showed filamentous anaerobic bacilli. Colonies grown were small (2 mm.), low convex, translucent, greyish, sticky and butyrous if touched with a loop. In subculture the organism became completely Gram-negative, pleomorphic and filamentous. Bacteriological and biochemical studies led to the conclusion that the organism belonged to the Fusiformis necrophorus species.

The organism was probably present in the vagina before delivery, and the rapid labor, by producing multiple lacerations, allowed infection of the venous sinuses to occur. As the result of anemia from hemorrhage, resistance would be subnormal and multiplication could more readily take place. 1 chart.

encephalitis and nearly all within the first 2 years. Gamma globulin for the prevention or mitigation of measles, and earlier vaccination against pertussis, are important. The use of hyperimmune serum for treatment of pertussis in infancy, plus prompt use of oxygen and other measures, would probably reduce the number of cerebral accidents.

Of the noninfectious factors, trauma to the head is most important. This emphasizes the importance of watching carefully and for a sufficient period, with subdural hemorrhage in mind, those children who have suffered head injuries. One 9-months-old child suffered a period of anoxia, probably about 5 minutes, in a reaction to a dose of "mecholyl chloride"; 3 months later he had generalized cortical atrophy.

Although accurate appraisal is impossible, the data suggest in $\frac{1}{3}$ of the cases the probability, and in $\frac{1}{4}$ a possibility of prevention. In about 40 per cent nothing preventable could have been done. For the remainder, information is too incomplete to permit judgment.

While more knowledge and improved technics are needed, there is also need of a much wider dissemination and adoption of the knowledge of basic principles and technics already available, of more and better education and standards of practice, and of more contacts and conferences between obstetricians and pediatricians. 5 tables.

PREMATURITY—AN ORIENTATION

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Premature births consitute at least 5 per cent of the total births in the United States—in 1944, e. g., over 150,000 premature infants. If birth weight of 2500 gm. or less is used as the criterion, the percentage is probably much higher; in New York in 1939, 7.3 per cent of infants were premature on that basis.

A birth weight of 2500 gm. or less is the best criterion for prematurity based both on clinical indications for special care and on the sharp contrast in mortality above and below this figure. Eastman found at the Johns Hopkins Hospital a fatality rate (percentage of deaths among infants born alive) of 0.4 per cent among mature infants (those weighing at birth 2500 gm. or more), compared with 10.7 per cent for premature infants (those weighing 1000–2500 gm.). Even among infants weighing 2000–2500 gm. the fatality rate was 10 times that for mature infants.

The question of setting a lower weight limit to differentiate premature live births from abortions is more difficult. The American Academy of Pediatrics recommends that all *live-born* infants weighing 2500 gm. or less at birth should be classified as premature.

The importance of Rh incompatibility, demonstrated in 4 cases here, in producing cerebral damage is well known. The exact cause of the cerebral injury and its frequency in relation to all erythroblastosis are not known; it seems not to be dependent on the amount of anemia. It is more likely that the damage may be due to the profound changes in the placental villi which may interfere with the exchange of oxygen and perhaps other substances, leading to anoxic damage.

Only a minority of these prenatal factors can be considered preventable at present. Certainly Rh-positive blood should never be used for transfusions in girls and women not known to be Rh-positive. Some authors suggest that when Rh antibodies appear in the maternal blood only relatively late, early induction of labor may save damage. Women with cardiac disease likely to cause decompensation should be advised not to have babies; if they do, every effort should be made to avoid decompensation, and if it occurs every effort including oxygen should be made to offset anoxia. Oxygen is of course especially important to the pregnant woman with pneumonia. Since no active prevention of rubella is as yet available, exposure of young girls to this nearly always mild disease might perhaps be encouraged.

Outstanding among paranatal factors is the large number of difficult deliveries, of breech presentations and of abnormalities of the cord, all of which menace the oxygen supply to the infant and some of which favor intracranial hemorrhage. The newborn infant's relative immunity to anoxic damage probably extends not much over 15 minutes. The need of increased oxygen supply to the mother, or at least avoidance of reduction, must be kept in mind. Nitrous oxide is a very serious danger here. It would be preferable if nitrous oxide in obstetrics were discontinued; but at least the need for 15 per cent or more of oxygen, as indicated by Eastman, must be insisted on. Sedation was recognizably heavy in 6 of these cases. Oxytocics in the case of overdosage or of idiosyncrasy may cause prolonged uterine systole with reduction in uterine blood flow and oxygen supply. The use of quinine as an oxytocic may possibly produce deafness in the infant.

While intracranial hemorrhage is perhaps a far less common cause of cerebral atrophy than simple anoxia, its occurrence and importance are undeniable. If recognized in time, subdural hemorrhage can be remedied and its sequelae prevented by operation. Subdural puncture will provide the diagnosis if one is alert to the indications, and operation can be done to advantage during the neonatal period.

At birth, prolonged apnea or cyanosis, requiring resuscitation, is an important factor. Use of the laryngoscope for removing under direct vision occluding plugs of mucus, and liberal administration of oxygen, are important advances. Premature infants run a special anoxic danger, apparently related to the immaturity, but often the best modern methods, including clearing of the airways, use of oxygen, transfusions and administration of ascorbic acid will succeed in preventing damage. Neonatal hypoprothrombinemia, fortunately rare, is theoretically preventable by vitamin K to mother or infant, but prompt transfusion seems more effective.

Postnatally, infection is responsible for nearly $\frac{2}{3}$ of the cases, about half due to

A PREMATURE SURVIVAL INDEX AND THE CONDUCT OF PREMATURE LABOR

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There is today no unanimity as to precisely what constitutes a "premature infant". Various criteria are in use to determine whether a fetus is viable. Thus, on the basis of duration of pregnancy, a fetus which has remained in utero twenty-eight weeks is generally said to be a premature. The lower limit of prematurity recognized by DeLee is twenty-six weeks' gestation. The Catholic church, too, recognizes a fetus from a twenty-six weeks gestation as being premature.

Another standard for prematurity, and the one most commonly used, is birth weight. The generally accepted weight limits for prematurity are 1,500 gm. (3.3 pounds) and 2,499 gm. (5.5 pounds). The lower limit is of particular concern to us. There are a fair number of fetuses of gestation of at least twenty-eight weeks with birth weights below 1,500 gm., even some below 1,000 gm. (2 pounds 3 ounces). This occurrence is frequent enough to have prompted Haas to suggest 1,000 gm. as the lower weight limit of prematurity. Naturally, those premature infants with birth weight below 1,000 gm. have a very poor expectancy for life, yet it is interesting to record that there are at least 54 surviving cases on record. With the above facts in mind, it becomes quite obvious that birth weight is indeed a very poor criterion of prematurity. We must remember that birth weight of the newborn is an index of the weight of its ancestors and, since there are very wide ranges in weights of adults, there will accordingly, be great normal variations in weights of newborn infants, whether they are born prematurely or at or near term. Again, some maternal diseases, notably chronic nephritis, have a very detrimental effect upon fetal nourishment, and frequently cause children to be produced far below the birth weight normally expected for the period of gestation. The ease in rearing these, if born alive in good condition, corresponds to the advanced gestational period and not to the sub-normal birth weight. In other words, they do not afford the difficulty found with premature infants of the same weight born of non-nephritic mothers. Three of the above noted 54 raised premature infants with weights of less than 1,000 gm. were reported by Haas, and it is an interesting commentary that two of these three were born of nephritic mothers. Occasionally one finds very marked differences in birth weight of a pair of identical twins. An outstanding example of this was noted by one of the authors when single-ovum twins were delivered at thirty-three weeks' gestation with one weighing 1,005 gm. and the other 2,260 gm. The smaller was raised with very little more difficulty than the larger.

Still another standard for determination of prematurity is body length. Crown-heel length or standing height is commonly used. The generally accepted

The trend of neonatal death rates, both those from all causes and those with prematurity as a primary cause, for the 11 years 1934–1944, has been steadily downward.   The total rate has dropped from 34.1 to 24.7 per 1,000 live births, and deaths from prematurity from 15.6 to 11.5.   The downward trend is apparent for both white and non-white premature infants, although the rates for non-whites are much higher and decline more slowly.   Hospital fatality rates also offer some evidence that improved methods of diagnosis and treatment, as well as general care, have reduced the percentage of deaths in all weight groups except those below 1,000 gm.

Premature birth accounts for almost half of neonatal deaths.   Some have died because they were too immature; others because of anoxia, birth trauma, or congenital malformations not diagnosed; and some through inadequate care.

More than half the deaths of prematures occurred on the first day (1944 figures).   These deaths can be reduced by obstetric use of analgesias and anesthetics that will not result in fetal anoxia, by improved methods of resuscitation, and by conservation of the infant's body heat and administration of oxygen.

Over $\frac{1}{4}$ of the deaths occurred from the second to the seventh day. Skilled medical and nursing care, suitable environmental conditions including temperature control and added oxygen, suitable feeding and fluids, and proper care of neonatal diseases will reduce these deaths.

From the end of the first week to the end of the first month only 11 per cent of the deaths occurred.   These are largely due to infection, and are preventable. The proportion of deaths of prematures from 1 month to 1 year is very small.

Prevention of premature labor or prolongation of pregnancy till the fetus weighs at least 1500 gm. (keeping in mind the mother's welfare) will do much to reduce the morbidity and mortality from premature birth.   Adequate prenatal care is important both in the incidence of premature birth and in the proportion of prematures who die.   In some women with cardiac conditions, for instance, cardiac consultation throughout pregnancy is important and is successful.   With adequate prenatal care, severe toxemia and eclampsia do not occur.

For a fairly large proportion of premature births no cause is determined. Poor nutrition, overwork, emotional disturbances, and so forth, may be involved. A statistical relationship appears between poor environmental conditions and economic status on the one hand and higher incidence of premature births on the other.

Only a small proportion of infants weighing less than 1000 gm. at birth can be expected to survive, even with above average care.   But above 1000 gm. the survival rate increases sharply, and 94 per cent of those in the 2000-2500 gm. range should survive.   Studies indicate that the fetal rate of growth is only temporarily interfered with by birth.   Comparisons of weight and height of premature with mature infants must be corrected for conceptional age until the premature catches up, which tends to be from near the end of the first to the fourth year or later.   In regard to mental development, prematures who do not suffer intracranial injury compare favorably with the mature infants, with allowance for conceptional age until the premature infant attains maturity.   6 tables, 3 figures.

the infant was the heaviest and the longest in the series, these latter two factors helping to produce the largest index. In this connection, it should be pointed out that the mother menstruated regularly every twenty-eight days, and that she first perceived fetal movement at a time which would tend to confirm the accuracy of her menstrual history. In the lower index bracket was found Case 20 which is believed to have been one of the longest retained in utero in this series.

It is these apparent inconsistencies in one or more of the commonly employed criteria of prematurity which the authors believe will be overcome by the use of a sizable number of factors such as offered by their five-point premature survival index.

Suggestions for the obstetrician's contribution in reducing the premature infant mortality rate are given. These include: avoidance of analgesia after the onset of true labor in the period of prematurity, the use of local or regional anesthesia for premature delivery, preservation of the integrity of the fetal membranes through the second stage of labor, maintenance of maternal-fetal circulation as long as possible, and the prophylactic use of chemotherapy in premature labor.

(This is a worthwhile idea but as the authors realize, a much larger series of cases will be necessary to establish its value. Although weight sometimes leads to very inconsistent results in the determination of prematurity, it is generally recognized as the most valuable index for general use for the very good reason that it is the only criterion which can be ascertained routinely with accuracy. As far as length is concerned, this is very possibly a more reliable index of prematurity than weight provided it is determined with some degree of precision, but take a sleepy interne at 3 A.M. and a wriggling baby, the accuracy of the procedure frequently leaves much to be desired. In regard to menstrual history, the dependability of this criterion will rest in large measure on the intelligence of the patient; thus, in a substantial number of our colored women the menstrual data are quite worthless.

I presume that it is the authors' intention to employ their index for statistical purposes in the evaluation of their results in bringing up premature infants. They would doubtless agree that it would probably be of minor assistance only in individual cases because here clinical signs are of more prognostic value, namely ability of the baby to get along without oxygen, presence of cyanosis in and out of oxygen, sternal retraction, temperature stability, ability to take feedings, etc.—Ed.)

THE LIMITED VALUE OF MICROSCOPY OF LUNG TISSUE IN THE DIAGNOSIS OF LIVE AND STILL BIRTH

H. A. SHAPIRO

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Clin. Proc. Cape Town Postgraduate Med. Assoc., 6: 149–158, 1947

By way of background the author notes that authoritative reference works deal in rather ambiguous manner with the microscopic appearances of the lungs of stillborn infants and of those who have breathed. Thus, Gibberd states: "Before birth the alveoli of the lungs are completely collapsed and their walls

limits of this criterion for prematurity in most teaching institutions are at least 35 cm., but less than 45 cm. total length. When we realize that body length is an hereditary factor, it is immediately apparent that this standard is reliable only in children born of parents of average height. Anyone who has measured the length of many newborns, and especially anyone who has remeasured some by the same or by various methods, will recognize certain inherent difficulties in the precise determination of this diameter of a newborn.

Not infrequently more than one standard is utilized in order to ascertain the presence of prematurity. For example, Dana defines the premature infant as one whose birth weight is between 1,500 and 2,499 gm., or whose total length is between 35 and 44.9 cm., regardless of duration of pregnancy. This combination is fairly commonly employed in teaching institutions.

From the foregoing, it appears quite obvious that there are several criteria in use for the diagnosis of prematurity, but that all are variable factors. It has occurred to one of the authors that a combination of a larger number of factors in the small premature infant should produce less inaccuracy in the diagnosis of prematurity and in prognosticating the probable outcome than has thus far been possible with any of these factors used alone. The assumption is that the inaccuracies in single factors will tend to be equalized when combined with each other. Accordingly they have developed an index for prematurity from a combination of five factors.

Only twenty-three premature infants thus far comprise the series. They are nonselected, but consecutive private cases delivered at St. Joseph's Maternity Hospital over a period of ten months. Stillbirths and those succumbing in the immediate antenatal period are not included.

The factors used to establish the five-point premature survival index are the following: (a) gestational period is calculated from the first day of the last normal menstrual period regardless of regularity or irregularity of the menstrual cycle in each instance. In the current series the cycles varied from twenty-eight to thirty-two days with one exception, in which the cycle was forty-five to sixty days, and nothing is known of the cycles of three other patients. (b) Weight of the newborn was obtained in ounces. (c) The total, or crown-heel, length was obtained in inches in the usual manner, i. e., by measuring with a steel tape along the side of the body suspended at the ankles. (d) Occipito-frontal circumference was recorded in inches. (e) The circumference of the chest was obtained at the level of the xiphosternal joint and recorded in inches.

The index was obtained by adding gestation in weeks, weight in ounces, crown-heel length in inches, head circumference in inches, and the chest circumference in inches, and then dividing the total by five. This resulted in indexes ranging from 19.2 to 25.7 for the twenty-three infants.

All premature infants with an index of at least 21.0 were raised, whereas only 50 per cent of those with a smaller index survived. Of particular interest in this series was the absence of correlation between gestational period, birth weight, and total length of the infants. An outstanding example of this was seen in Case 5 where the gestational period was said to have been only 29½ weeks, whereas

the infant was the heaviest and the longest in the series, these latter two factors helping to produce the largest index.   In this connection, it should be pointed out that the mother menstruated regularly every twenty-eight days, and that she first perceived fetal movement at a time which would tend to confirm the accuracy of her menstrual history.   In the lower index bracket was found Case 20 which is believed to have been one of the longest retained in utero in this series.

It is these apparent inconsistencies in one or more of the commonly employed criteria of prematurity which the authors believe will be overcome by the use of a sizable number of factors such as offered by their five-point premature survival index.

Suggestions for the obstetrician's contribution in reducing the premature infant mortality rate are given.   These include: avoidance of analgesia after the onset of true labor in the period of prematurity, the use of local or regional anesthesia for premature delivery, preservation of the integrity of the fetal membranes through the second stage of labor, maintenance of maternal-fetal circulation as long as possible, and the prophylactic use of chemotherapy in premature labor.

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are in apposition, and there is not any space in any part of the lumen of the bronchial tree." (Short Textbook of Midwifery, 3rd Edit. 1943, Churchill, London, p. 497.) Similarly, Farber and Wilson observe that "microscopic sections of the lungs of the newborn baby who has never breathed show that the terminal bronchioles and the alveolar ducts possess definite though very small lumens. The connective tissue of the lungs appears very prominent in contrast to the unexpanded alveoli. The alveoli may have tiny slitlike openings, or, in many cases, the spaces may not appear definite, owing to the encroachment of the large cuboidal lining cells." (Am. J. Dis. Child. 46: 572, 1933.)

Such accounts together with accompanying illustrations would indicate that, histologically, unrespired fetal lung has an almost glandular appearance with no well developed alveolar spaces. In order to investigate the status of the pulmonary alveoli of the fetus in respect to whether or not respiration has taken place, the author has studied 30 cases histologically and has compared his findings with the hydrostatic test, that is, whether the lung sinks or floats in water.

The conclusion reached is that current histological criteria in regard to respiration are unacceptable because they are misleading. The difficulties appear to have risen from a failure to appreciate the normal embryological changes which gradually occur in the course of the development of the respiratory tract of the human fetus. In many cases of stillbirth at or near full term, the lungs show definite evidence of alveolar space formation although no single part of the lungs floats in water. In the course of fetal development there is a gradually evolving change in the structure of the respiratory tract, starting off with the well-known budding of subsidiary ducts surrounded by a fairly dense connective tissue. In the later, but still antenatal, stages this process goes on to the formation of alveoli containing well-defined spaces with relatively thin walls, this growth occurring in the absence of extrauterine development or respiration. In regard to the role of intrauterine respiratory movements in production of these changes, the author regards them as ancillary only and believes that for purely embryological reasons the lungs at or near full term will have reached such a stage of development that their microscopic appearances will not differ appreciably from the appearances of the lungs of a newly-born infant which has lived and breathed and whose lungs float in water.

The author documents the above statements not only by photomicrographs from his own series of human fetuses but also by photomicrographs from a similar study made by Ham and Baldwin on pig fetuses. (Anat. Record, 81: 363, 1941.)

(This report is in keeping with the findings of Edith Potter which were published some years ago but which need reiteration. Her extensive observations on the fetal lung are clearly summarized and convincingly illustrated in the well-known little volume, Fetal and Neonatal Death by Potter and Adair, Univ. Chicago Press, Chicago, 1940, pages 35–44. She compares the pattern of the alveoli at the time of normal birth to that of a partially crumpled paper sack; in other words the alveoli are not completely distended as they will become some days after birth, but neither are they completely collapsed. On the basis of her photomicrographs, the very similar ones of Shapiro, and others I have ⌐ ˙ would

appear that with complete intrauterine development of the lung at or near term, the total
volume occupied by the alveolar cavities is rather more than that occupied by the septs.
That this state of development may occur without the distending effect of anything intro-
duced from without is shown by 2 remarkable cases which Potter reports. "The first was
an infant apparently normal at birth but in whom respiration could not be established.
Necropsy demonstrated a cartilaginous obstruction of the larynx complete except for an
anterior channel of such narrow caliber that it was definitely visible only with a dissecting
microscope. The lungs were large and the alveoli were well developed. The second case
was an infant who died soon after birth in whom, among other anomalies, an accessory lobe
of lung tissue was present, completely cut off from the remainder of the lung and entirely
separate from the bronchial tree. The alveoli in this portion seemed normally developed
and similar to those in the normal lung."—Ed.)

AN EPIDEMIC OF DIARRHEA IN A NEW-BORN NURSERY CAUSED BY PSEUDOMONAS AERUGINOSA

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This is a report of an epidemic of diarrhea in 24 newborn in which there were
9 deaths. Eighteen probably contracted the disease in the newborn nursery.
One was discharged, returned to the hospital as a feeding problem, and developed
diarrhea 7 days later. Five developed diarrhea at home after being in contact
with a case in the family.

Diarrhea was the first and often the only symptom, recurring over periods as
great as 6 weeks. Vomiting, dehydration, cyanosis, collapse, pain and fever
followed in that order.

The infecting organism was Pseudomonas aeruginosa which gained entrance
to the milk supply through water which was dripping off a rag into the pas-
teurized milk of 1 dairy. Bottles of dairies were exchanged without proper clean-
ing and sterilization, so that the organisms easily gained access to the other
dairies. The contaminated milk caused an epidemic of gastroenteritis in the
town and caused outbreaks among patients and employees of the hospital and
in consumers of the milk in outlying towns.

The infants were secondarily infected by mothers and nurses who drank the
milk in the hospital, or by other members of the family after they were sent
home.

Apparently well persons who had ingested the contaminated milk acted as
temporary carriers. (Eberthella typhosa was also isolated from one of the
nurses.)

Twenty-four infants were studied clinically, and 9 of these bacteriologically.
Pseudomonas aeruginosa was isolated in the stools of all 9. Autopsy material
was obtained from 2 cases and Pseudomonas aeruginosa was isolated from both.

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OPERATIVE OBSTETRICS

THE CHOICE OF ANESTHESIA FOR OBSTETRIC AND GYNECOLOGIC PATIENTS

John S. Lundy

Choice of anesthesia has been most recently influenced by curare (intocostrin —Squibb), which produces muscular relaxation affecting in order the ocular and facial muscles, the neck, gradually the thorax and abdomen, and lastly the diaphragm. The drug is given intravenously, 1 cc. or 20 mg. per minute until the respirations become shallow and do not increase when injection is stopped for a minute or two. Small doses may be repeated as needed. Overdoses of curare are combated with artificial respiration with or without neostigmine (prostigmine) or physostigmine—1 to 4 cc. prostigmine in 1:2000 solution intravenously, 1 cc. solution to neutralize each 1 cc. of the last dose of curare.

Although curare is not recommended for nonoperative obstetrics, it may be used in operative obstetrics, combining a moderate effect of curare with light surgical anesthesia which may be increased or decreased as needed. The drug has been used with cyclopropane, nitrous oxide and oxygen, ethylene and oxygen, and with pentothal sodium (with or without oxygen), or with ether anesthesia in reduced doses and ether mixed with gases. It might reasonably be used with regional anesthesia also. Whitaker has reported no noticeable effect on the baby from curare used in abdominal cesarean sections. Miscarriage is not likely as a result of curare, nor from anesthetics, especially spinal and inhalation agents; use by rectum of ether or avertin may be doubtful, since they may produce severe rectal cramps.

Intravenous anesthesia, especially pentothal sodium, has a place in surgical obstetrics, and wide application in gynecology, where it may be used to make induction of anesthesia less unpleasant in such operations as dilatation and curettage. A barbiturate if used for the nonsurgical obstetrical patient is better given orally. Recently demerol has been used, usually in 100 mg. doses at 3-hour intervals, a primipara perhaps needing 3 doses, and seems useful. Regional anesthesia is relatively new and can be used in many instances. Caudal anesthesia (procaine hydrochloride or metycaine, 1 or 1.5 per cent solution), administered by insertion of a catheter or of a needle into the caudal canal, will be associated with fewer untoward reactions on the unborn child than other methods, and produces spectacular results in the presence of eclampsia. It might be tried in $\frac{1}{4}$–$\frac{1}{3}$ of the average obstetrical cases, but the possible complications are too numerous and too fatal to allow its use by an inexperienced person.

With inhalation agents, a few breaths of a concentrated mixture or a number of breaths of a more dilute mixture can be given. The author likes nitrous oxide and oxygen, gradually increasing the concentration as pains become more severe

Treatment before isolation of the organism had consisted of penicillin, transfusions, parenteral fluids, and sulfa drugs; the last 2 were the most effective. Following identification of Pseudomonas aeruginosa, a review of the literature revealed that it produces small amounts of hydrocyanic acid, suggesting symptoms from slow poisoning. Methylene blue was therefore suggested as treatment, and 1 of the physicians used it with startlingly effective results.

Epidemiological milk sanitation, and bacteriological studies, and the results of use of methylene blue, thus all support the conclusion that Pseudomonas aeruginosa was the etiological agent. Control measures based on the findings were initiated:

1. Autoclaving all milk, till a safe supply could be obtained.

2. Stool cultures on mothers 2 weeks before they entered the hospital; cultures repeated upon entry, with questioning concerning a history of diarrhea.

3. When there was a positive culture or history, or when diarrhea developed during hospitalization, the mother was isolated on a separate floor and the infant isolated from both the nursery and the mother. If a history of diarrhea or a positive stool culture was obtained before entrance, the mother was delivered in her own room.

4. Isolation of mother and infant, as above, and immediate notification of the physician, on first suspicion of diarrhea in an infant.

5. Another room set up as nursery for all new infants, until all in the original nursery had been discharged and the nursery thoroughly cleaned.

6. All mothers and infants sent home on the fourth day routinely; public health nurse notified to visit and give instructions on care and prevention of infection. If infant showed signs of diarrhea on fourth day, he was sent to pediatrics instead of home. If infant and mother had to stay more than 4 days, they were placed in a private room and the infant kept out of the nursery.

7. Public health nurses assigned to assist all mothers leaving the hospital with newborn infants, to adopt every precaution.

8. Stool cultures repeated on all nurses in the nursery; pending report, all who had had diarrhea in the last month removed from the nursery.

The epidemic subsided within 3 weeks after these measures were put into effect. 1 table.

the steep Trendelenburg position is so often used.   Rectal anesthesia is no longer indicated.   For the pregnant woman who requires an abdominal operation, any agent, except the rectal method, may be used.

THE GENERAL PROBLEM OF ANESTHESIA IN OBSTETRICS

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Minn. Med. 30: 953–955, (Sept.) 1947

Factors to be considered in the choice of any general or local anesthetic, analgesic, or amnesic agent include (1) the physiopharmacological action of the agent on both maternal and fetal structures, (2) any existing fetal or maternal diseases or abnormalities, (3) what agent or agents and method are best suited to the emotional and physical status of the mother, and (4) whether the method is the one of greatest safety to the mother and the infant.

The agent should possess adequate properties to obtund the pains of labor without any untoward systemic effects.   It should also be reasonably prompt in its action and should have no cumulative effects.   Finally, effective counteraction for an overdose or idiosyncrasy to the agent should be available.

The wisdom of attempts to relieve the pains of labor totally have been seriously questioned, from the psychological as well as other viewpoints.   DeLee and Greenhill have emphasized repeatedly the price that is paid to make childbirth painless.

Many methods of analgesia and anesthesia have been proposed, but some are highly technical and complex.   In the average uncomplicated labor, obstetrician and anesthesiologist, singly or together, focus attention on agents which will obtund pain and produce at least relative amnesia.   In the first stage of labor analgesic and amnesic agents usually suffice.   In the second and third stages anesthetics are as a rule required.   The following comments on the agents are a composite opinion.

In the first stage, at present, "scopolamine in conjunction with a barbiturate such as pentobarbital sodium is one of the most effective combinations.   The dose of scopolamine is $\frac{1}{50}$ or $\frac{1}{100}$ grain (0.00043 or 0.00065 gm.) hypodermically administered when labor pains are well established and regular and there is effacement and beginning dilatation of the cervix.   Simultaneously $1\frac{1}{2}$ to 3 grains (0.1 to 0.2 gm.) of pentobarbital sodium are given orally.   The administration of scopolamine is repeated about one hour after the initial injection.   Some authorities recommend three doses of $\frac{1}{100}$ grain (0.00065 gm.) of scopolamine alone subcutaneously administered at intervals of half an hour when labor is established. The duration of action of scopolamine is about 2 hours in the dose mentioned. In prolonged labor additional amounts of scopolamine may be required at inter-

till reaching nitrous oxide 90 per cent and oxygen 10 per cent. If there is not enough relief of pain, he changes to ethylene 80 per cent, oxygen 20 per cent, progressing to ethylene 90 per cent and oxygen 10. The low percentage of oxygen is usable only because the patient takes but a few breaths of the mixture. As soon as one begins maintenance of continuous surgical anesthesia, the amount of oxygen is increased, and often, just after delivery of the head and shoulders, twice the usual amount of oxygen may be given for a few breaths, in hopes of benefiting the baby.

Moore believes the barbiturates should not be used as the only anesthetic in labor, and their intravenous use should be restricted to pre-eclamptic toxemia or eclampsia. In small doses they are very helpful for the nausea and vomiting of pregnancy, or the insomnia of late pregnancy. His favorite technic in the average normal labor is as follows:

"When the patient begins to complain of pain in labor, she is given morphine and scopolamine stable (Roche) 0.00066 gm. by hypodermic or 2 capsules of *pentobarbital sodium (0.198 gm.) by mouth. The room is darkened and all* unnecessary manipulation of the patient is prohibited. From 45 minutes to 1 hour after the foregoing injection she is given scopolamine stable (Roche) 0.00066 to 0.00033 gm. by hypodermic, depending on her reaction to the first injection. At intervals from 1 to 2 hours thereafter she is given scopolamine stable (Roche) *0.00033 gm. by hypodermic until the first stage is well advanced.*

"At this time sodium amytal or pentobarbital sodium is given as a retention enema. This produces a condition bordering on obstetric anesthesia in from 20 to 30 minutes and its effect persists for from 1 to 2 hours. I have found occasional instances in which delivery is effected without the aid of any inhalation anesthetic, though usually ethylene-oxygen or, occasionally, cyclopropane-oxygen, are added for the actual delivery."

For minor gynecological operations one may use intravenous pentothal sodium or a gas with a small amount of ether. Pentothal sodium, preferred by most patients, calls for preliminary medication, usually morphine with atropine, at least 1 hour before operation. A small amount of barbiturate, e.g., 0.1 gm. pentobarbital sodium, the night before operation and in the morning reduces the amount of pentothal sodium necessary; the use of 50–50 nitrous oxide-oxygen with the pentothal sodium reduces the needed amount still further, besides providing additional oxygen. Nitrous oxide-oxygen plus ether, another gas with or without ether, or curare plus an inhalation agent may be used, following 1–1.5 gm. pentothal sodium.

Spinal anesthesia is often preferred for pelvic operations. Most obese patients stand spinal anesthesia very well, but a few, when they show considerable vasomotor collapse resulting, are extremely difficult to support. Best support is blood transfusion, perhaps with some vasopressor substance with the first portion to avoid a damaging anoxia. Curare helps produce relaxation in the obese patient with fewer cases of collapse than when spinal anesthesia is used alone; however, the drug is too new for possible drawbacks to be known.

An intratracheal tube is particularly desirable for adequate ventilation because

definite place in obstetric anesthesia. Low spinal or saddle anesthesia with hyperbaric solutions, using any of several local anesthetic agents, is becoming more and more widely employed. If procaine hydrochloride is used, 50–75 mg. are dissolved in 2 cc. of 10 per cent solution of dextrose. After a lumbar puncture at the level of the third and fourth lumbar interspace, this mixture is diluted with an equal volume of spinal fluid and injected slowly, with the patient in the sitting position. Anesthesia is quickly established and lasts for 1 to 1½ hours. Postpartum bleeding is diminished and the babies have little if any respiratory or circulatory depression.

Cesarean section presents a difficult problem. Prolonged general anesthesia may produce fetal respiratory depression and often death. Improperly controlled spinal anesthesia has been disastrous. Many authors have advocated local infiltration or block anesthesia of the lower abdominal wall plus inhalation or intravenous anesthesia at the time the uterus is opened. If the timing is correct, little if any fetal depression occurs. The mother's objection to the procedure is the main obstacle.

Continuous caudal anesthesia, utilizing posture to advance the anesthesia high enough, and continuous spinal technique will if carefully performed permit safe and satisfactory results. There is usually less blood loss in cesarean section with local, caudal or continuous spinal than with inhalation anesthesia. If inhalation anesthetics alone are used, cyclopropane is best as far as the baby is concerned, but resuscitation procedures are much more common than with regional or combinations of regional and general methods.

In the presence of certain outstanding complications—hypertensive cardiac disease, nephritis, pre-eclampsia and eclampsia, pernicious anemia, leukemia, and other blood dyscrasias, including hemorrhagic diathesis—local or regional anesthesia is to be preferred to general anesthesia, particularly with ether, chloroform or avertin.

The aim should be to make pain of the parturient as easy as possible, constantly keeping in mind the safety of the newborn and of the mother.

SODIUM PENTOTHAL ANESTHESIA FOR SELECTED VAGINAL OBSTETRICS

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Between July 24, 1945 and October 1, 1946, 350 patients from both ward and private services of the Hermann Hospital were delivered of viable pregnancies under intravenous sodium pentothal anesthesia. The material used was pro-

vals of 2 hours." One drawback is the occasional occurrence of extreme excitement and stimulation of the patient, necessitating constant nursing attention.

Another combination having more analgesic effect as well as amnesic action is scopolamine, barbiturates and demerol. Several investigators have shown that demerol and scopolamine together cause less fetal respiratory depression than this combination plus a barbiturate. "A suggested regimen with these agents is the hypodermic injection of 100 mg. of demerol along with $\frac{1}{150}$ grain (0.00043 gm.) of scopolamine when the labor pains are strong and regular. If these 2 agents are not quite sufficient a barbiturate can be given orally or rectally as a supplement. The administration of demerol and scopolamine may be repeated at intervals of 3 to 4 hours."

Morphine and pantopon should in general not be used within less than 2 hours from the time of delivery, since they cause fetal respiratory depression. When a general anesthetic agent follows, the incidence of asphyxia neonatorum is definitely increased, especially in prematures.

Rectal analgesia is well-accepted and liked by many. Ether in oil (65 per cent ether—35 per cent oil), the original Gwathmey technique, has been modified to include paraldehyde, avertin, chloral hydrate, and pentothal sodium as rectal analgesics. Intravenous anesthesia is not recommended, as a rule, because of its rapid and concentrated action on fetal and maternal respiration. Inhalation anesthetic agents both volatile, such as ether, chloroform and divinyl ether, and gases, such as nitrous oxide, ethylene, and cyclopropane, have been used in various techniques, but are usually given during the second stage of labor when anesthesia rather than analgesia is required.

Though multiparous women frequently give birth spontaneously with only the basic analgesic supplied, some form of general or regional anesthesia is required in the second and third stages in most cases. Drop ether and chloroform are used extensively, particularly in home deliveries. Where an anesthesiologist is available, many combinations may be used. During delivery when the presenting part distends the perineum the depth of general anesthesia should be carried to plane 1 or 2 of the third or surgical stage of anesthesia, at which level uterine contractions are not abolished but episiotomy and application of forceps can be done without pain. Nitrous oxide usually requires the addition of ether vapor to provide safe anesthesia in the second and third stages of labor. Concentrations of nitrous oxide greater than 80 per cent along with 20 per cent oxygen should be avoided. Cyclopropane and ethylene, administered carefully by the closed technique, are best suited for the terminal stages of labor.

Many procedures of varying complexity have been used for regional anesthesia, including pudendal block, transsacral block, paravertebral block, caudal block, local infiltration, and low spinal anesthesia. Tucker and Benaron, Cleland, Lull and Hingson, Lundy and Tovell and others have described their techniques, their merits well established. Pudendal nerve block, e.g., is a successful type for many obstetric operations including spontaneous delivery, low forceps application, episiotomy and perineorrhaphy. Hingson and associates have shown that the continuous caudal method, used by trained people, has a

abandoned for intravenous sodium pentothal when the patient was declared "too uncooperative" (2 cases), when an unfavorable fetal position was discovered at vaginal examination (2 cases), and when 1 delivery was unduly prolonged due to fetopelvic disproportion. Actually, the supplementary anesthesia given was rarely the result of failure of pentothal anesthesia.

Intravenous sodium pentothal anesthesia, as noted previously, does not affect uterine contractility or contractions. The average estimated blood loss in this series of deliveries was 168.4 cubic centimeters. Intravenous sodium pentothal anesthesia does not increase blood loss in the placental stage. Neither does it appear to decrease the amount of bleeding in that stage.

Two hundred and seventy or 77 per cent of the newborns required no resuscitation whatsoever, i.e., cried or at least breathed regularly and promptly after delivery. Forty-four or 12.5 per cent required little or only slight resuscitation. In these, aspiration of mucus or amniotic fluid was followed by mild cutaneous stimulation in the form of rubbing the back or thumping the toes or fingers. Pure oxygen was administered to 9 of these, but in each instance it is stated that resuscitation was of minor importance. That pentothal was responsible for apnea in these is far from proved. Actually in one the drug could not have played a role, for the child was born before the patient could be completely anesthetized. However, in 9 instances the newborn is said to have been mildly narcotized, in 2 there was a loop of umbilical cord about the fetal neck, in 1 mild cyanosis, in 2 much aspirated amniotic fluid, and in the remaining 30 there was no recorded or recognizable reason for the mild initial apnea. Analgesic drugs appear to be involved especially in the light of their frequent administration late in labor. However, all the above 314 newborns (89.5 per cent) requiring little or no resuscitation were actually born alive in good condition and survived the immediate neonatal period with a single exception—1 requiring no resuscitation, found dead in its crib 6 hours after delivery, believed to have suffocated, in which autopsy revealed only adrenal hemorrhage.

There remain 37 infants, 10.5 per cent of the series, in which minor degrees of resuscitation were inadequate. All but 1 of the infant deaths are included in this group. In no case did sodium pentothal per se appear to play any serious role in resuscitation or in survival of the newborn. The most serious effect of pentothal in this series was noted in a second twin delivered by midforceps extraction whose mother had been anesthetized for 16 minutes before this co-twin was born. The newborn was obviously narcotized and required moderate resuscitation but survived and was apparently undamaged. One could hardly expect ill effects upon the newborn with delivery planned to be completed within 8 minutes of induction of pentothal anesthesia. The records are not adequate enough to show the time interval between induction of anesthesia and delivery of the child, but it is believed that 8 minutes was rarely exceeded and most often not nearly approached.

In the series, there were 10 infant deaths for an uncorrected total fetal mortality rate of 2.86 per cent. There is no reason to assume that pentothal anesthesia was in any way the cause of any of these infant deaths.

vided in a 2 ampule carton. One ampule contained 1 gram of sodium pentothal powder and the other 50 cubic centimeters of sterile distilled water from which the 2 per cent solution was freshly prepared for each patient. The special sets kept handy for this use contained two 20 cubic centimeter syringes, rubber tubing with adaptor for syringe and needles, and 3 needles—1 No. 18 and 2 smaller needles. A metal syringe holder was clamped to the side of the delivery table and the patient's arm fixed to an armboard. The patient was prepared in lithotomy and draped for delivery. The bladder was generally catheterized during the process of induction of anesthesia. The accoucheur designated when he was ready to proceed with the actual delivery. An antecubital vein was usually selected for puncture and the vein catheterized in order to reduce the possibility of extravenous injection. Two or 3 cubic centimeters of the 2 per cent solution were injected initially. The patient was then asked to count out loud and an additional 2 to 3 cubic centimeters injected every 20 to 30 seconds until the patient ceased to count, after which an additional 5 cubic centimeters were given. By this time the patient was generally ready for vaginal examination or delivery. At the slightest movement on the part of the patient, an additional 5 cubic centimeters of the drug was injected.

For spontaneous delivery this procedure was only slightly modified. With the onset of the uterine contraction selected for final delivery, induction of anesthesia was begun. The patient was encouraged to bear down with the pains until the fetal head began to crown and the accoucheur was able to reach the fetal chin. Then, as soon as obstetrical anesthesia could be obtained, he would proceed with spontaneous delivery aided by the Ritgen maneuver or possibly assisted by mild suprafundic pressure.

The great majority of these anesthetics were given by members of the department of obstetrics, about half by obstetrical residents. One hundred and ten fetuses (31.3 per cent) were delivered spontaneously under intravenous sodium pentothal anesthesia, 226 by low forceps, 11 by breech extraction and 1 by version and extraction. As previously stated, a 2 per cent solution of pentothal was administered intravenously. Only 21 (8.4 per cent) received more than 50 cubic centimeters (1.0 gm.). The largest amount given, 135 cubic centimeters (2.7 gms.), was for the Mexican woman with a contracted pelvis and an excessive-sized erythroblastotic stillborn (intrapartum death) delivered by prolonged and difficult low forceps extraction. The average for the series was 39 cubic centimeters (0.78 gm.). In large measure, the amount of anesthesia varied with the amount and recency of administration of analgesia. Of interest were the great variety of drugs and combinations of these used to obtain analgesia. It was rather surprising to discover that 182 patients, 58.7 per cent of those receiving analgesia, received the last dose of the analgesic less than 2 hours before delivery of the infant. Obviously, this fact must be remembered when noting the dosage of anesthesia required. It must also be remembered as a factor in the production of apnea in the newborn infant.

Fourteen patients (4.0 per cent) received supplementary anesthesia. In addition to these, perineal block was the original anesthetic agent which was

groups managed by standard techniques of systemic sedation and terminal general anesthesia, based primarily on a study of 3000 cases of caudal analgesia and 1000 controls, indicate the following results:

1. There is a marked reduction in the maternal death rate in cases reported of continuous caudal anesthesia, and a slight reduction in maternal morbidity.

2. Blood loss is diminished.

3. The involution of the uterus is expedited, and incidence of subinvolution is only half as great in patients delivering under caudal as under general anesthesia.

4. Incidence of initial postpartum catheterizations will be slightly increased, but the incidence of 4 or more per patient will be decreased.

5. There is a significant difference in the percentage of babies with delayed respiration and the percentage requiring an agent to induce respiration, in favor of those delivered under continuous caudal as compared with general anesthesia.

6. More infants delivered with caudal analgesia were breast fed, and more gained weight during the first 7 days.

7. Stillbirths were markedly reduced. The difference between the groups is significant.

8. Deaths in the first week of life were decreased in the caudal analgesia group. The difference is statistically significant for the white group, but not for the smaller sample of colored infants. For the total of both stillbirths and neonatal deaths, there is a statistically significant difference favoring caudal analgesia in the white group, but not statistically significant in the colored.

9. Figures available for prematures do not show a significant difference, but the sample is small.

Estimates indicate that these newer methods of delivery applied to the whole country would cut in half the present loss of infants through stillbirth and death under 1 week of age.

The technique has also been used successfully in surgery and therapeutics, including cesarean sections and orthopedic operations, control of pain from burns on the lower half of the body, nerve block for sciatica, and as an adjunct in treatment of essential hypertension, toxemias of pregnancy, and eclampsia, uremic convulsions and prolonged anuria, and peripheral vascular diseases of the lower extremities. 14 figures, 3 tables.

VARIATIONS OF THE SACRAL CANAL: THEIR SIGNIFICANCE IN THE ADMINISTRATION OF CAUDAL ANALGESIA

Mildred Trotter

Dept. of Anatomy, Washington University, St. Louis

Caudal analgesia involves 3 anatomical factors: that a needle enter the sacral canal through its hiatus, that puncture of the dural sac be avoided, and that the anesthetic solution reach a given level (determined by the parts to be rendered analgesic) of the vertebral canal.

There were no maternal deaths.

As used in a small series and in 2 per cent solution, the authors have found sodium pentothal safe for mother and child. Its margin of safety seems to be such that a careful obstetric resident can quickly master the technique of its administration and can give it with little risk to patients. As such, it appears to be ideally adaptable to emergency obstetrical use but perhaps not for the casual anesthetist. The authors are continuing to employ it in this manner and are convinced that it has a definite and permanent place in obstetrical anesthesia.

(Our series of deliveries under sodium pentothal anesthesia now exceeds 5000 and we agree with the authors that this agent merits an important place in obstetric anesthesia, especially for low forceps.—Ed.)

CONTINUOUS CAUDAL ANALGESIA IN OBSTETRICS, SURGERY AND THERAPEUTICS

Robert A. Hingson

University of Tennessee College of Medicine, Memphis, Tenn.

This is a review of over 200 papers in the world literature from 1901 to the present, on continuous caudal anesthesia, primarily in obstetrics. The gradual development of knowledge, including the use of the indwelling malleable steel needle, the ureteral catheter technique, and the continuous drip method, anatomical studies and the drugs to be used, is covered by numerous papers listed in the bibliography.

Continuous caudal anesthesia, which is designed to relieve intolerable pain and not the discomforts of early labor, controls completely the pains of the terminal portion of the first stage, the second and third stages, and the post-delivery repair in more than 90 per cent of cases. Pain relief was satisfactory in 95 per cent. Pontocaine 0.15 per cent through ureteral catheter by intermittent injection or continuous drip, for expected long labors, and 1.5 per cent metycaine or novocain through the malleable needle for short rapid labors, are begun when there is effacement and dilatation of the cervix beyond 5 cm. for primiparas and 3 cm. for multiparas, and strong pains of at least 30 seconds are occurring every 3 minutes. In some patients it is necessary to establish, temporarily discontinue, and reestablish the technique. The technique completely alters the process of labor as usually described and has almost doubled the incidence of operative deliveries by occiput posteriors, transverse arrests, and outlet forceps extractions. Relaxation of the perineum is complete, the patients are alert and cooperative, and there is still enough voluntary diaphragmatic force and abdominal power to assist in the expulsion of the baby. The tendency towards a drop in systolic blood pressure is one of the main hazards.

Comparisons of patients receiving continuous caudal analgesia with control

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The sacral canal, continuation of the vertebral canal, is curved like the sacrum, triangular in cross-section at the base and flattened toward the apex. It is formed anteriorly by the dorsal surfaces of the bodies of the sacral vertebrae over which extends the posterior longitudinal ligament, laterally and posteriorly by the roots and laminae of the vertebrae. Adjacent laminae are united, except at the base, where elastic yellow ligaments extend between the laminae of the fifth lumbar and first sacral vertebrae. The laminae of the fifth and often the fourth sacral vertebrae fail to meet in the midline, leaving the sacral hiatus, which is roofed by a prolongation of the supraspinous ligament (the superficial posterior sacrococcygeal ligament), subcutaneous tissue and skin, through which the needle must pass to enter the hiatus.

The funnel-shaped caudal end of the dura mater extends usually to the level of the body of the second sacral vertebra, where it contracts into a filament and continues through the sacral canal and onto the coccyx. Extensions of the dural sac surround each pair of spinal nerve roots to their level of union, about the level of the intervertebral foramina, just distal to the ganglion of the dorsal root. In the sacrum, the intervertebral foramina are short tunnels which provide communication between the sacral canal and the anterior and posterior sacral foramina.

The epidural cavity contains a large amount of fat, arteries, and a plexus of veins which communicate with both the cranial and pelvic cavities. When the caudal needle is pushed into the sacral canal neither the vessels nor the dural sac should be punctured. The anesthetic will thus be deposited in the loose fatty tissue through which it will extend superiorly and also laterally, beyond the intervertebral foramina.

A long hiatus implies a diminished distance between the apex of the hiatus and the dural sac. The level of the dural sac is also significant here. Inserting the needle near the base of the hiatus rather than the apex reduces the risk of puncturing the dural sac. When the dorsal wall is open or contains apertures, the caudal method is still feasible since the canal is completed by ligaments; but the nature of the ligaments may permit the tip of the needle to escape and result in a subcutaneous injection.

Examination of the dorsal wall of the sacral canal in 1227 bones disclosed that:

1. In 47 per cent the apex of the hiatus lies at a level superior to the lower third of the body of the fourth sacral vertebra.

2. In 25 per cent apertures in the bone are present in the dorsal wall.

3. In an unestimated percentage the palpable landmarks of the hiatus are masked by overgrowth or reduction.

4. In 5 per cent the anteroposterior diameter of the canal at the apex of the hiatus is 2.0 mm. or less (although the mean is 5–6 mm.).

The level of termination of the dural sac in cadavers revealed that:

1. In 46 per cent (of 56 bodies) the dura extends caudal to the level of the middle third of the body of the second sacral vertebra.

2. In 42 per cent (of 53 bodies) the distance between the apex of the hiatus and the dural sac is less than the mean distance (47 mm.).

The volume of the sacral canal and its outlets in 400 bones ranges from 12.0 cc. to 65 cc.

In cadavers injected with colored solution through the hiatus, 16 in a lateral-to-supine position and 33 prone, the solution reached levels varying throughout the extent of the column in both groups. 7 figures, 1 table.

INCIDENCE OF CESAREAN SECTION

AMY LOUISE HUNTER

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As a result of the increase in birth rate, there were 382,420 recorded live-born babies in Wisconsin in the most recent 6-year period, 1941–1946 inclusive. This approximates the 383,277 recorded live births in the 7-year period 1934–1940.

Total incidence of cesarean section has increased from 2.02 per cent of total deliveries of live-born babies in the first period to 2.85 per cent in the second. Highest incidence, 3.11 per cent, occurred in 1945.

Maternal deaths have sharply declined over the 13-year span. Although deaths associated with sections have decreased also, they now form a larger proportion of the total maternal deaths.

No data on stillbirths are available for the first period. In the second, 4.4 per cent of the stillborn babies were delivered by cesarean section.

Each year there has been an increase in hospital deliveries which has been much greater than the increased incidence of licensed maternity beds in hospitals. 1 table, 2 charts.

SOCIAL AND LEGAL ASPECTS

EXPERIENCE AND LESSONS FROM EMERGENCY MATERNITY AND INFANT CARE

NATHAN SINAI

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In 1942, a request for help in providing maternity care for the wives of members of the armed forces was sent to the Children's Bureau. Beginning with little preparation and with certain funds already appropriated under Title V of the Social Security Act, this movement to help developed into EMIC (Emergency Maternity and Infant Care)—the chief preoccupation of the Children's Bureau and of local maternal and child health divisions, accomplishing in 3 years about 1,000,000 completed maternity cases and over 100,000 completed infant cases.

In its first year (1943) EMIC faced the task of expending appropriations totaling over $25,000,000. As the problem increased, the activity eventually involved a large part of the medical profession and the general hospitals, over 1,000,000 families, and over $117,000,000.

Despite strong support, the Children's Bureau has never had unqualified acceptance. Since organization of EMIC was assigned to an old agency rather than a war-created one, on the basis that it was an expansion of an existing program, EMIC automatically became attached to old antagonisms and to a long series of precedents. With such an urgent need for speed and without guiding experience, it was certain that mistakes would be made and precedents violated.

The first difficulty lay in the established formula of federal-states relations. Here time must be expended lavishly for conferences, education, negotiations, and the federal agency must never attempt to dominate. But the urgency for speed and the movement of patients across state lines forced the program into being federal rather than federal-state in the usual sense. A detailed master plan to serve as a blueprint for state plans avoided months of negotiation.

The federal-state relations, regulations and then the changes of regulations on the basis of new experience, and the dual concern over the immediate task and future policy, were thus sources of difficulty. State departments, with an eye to the future, were disturbed by what they interpreted as domination. The fees involved, regarded as a pattern of post-war costs of maternity care, became very important.

EMIC cannot be regarded as a complete preview of a national health plan because of its emergency characteristic. But it does offer lessons which may be applied by national, state, or local plans.

The most crucial period in the existence of any large scale plan is the time before distribution of any service begins. At least a year should elapse between the decision to adopt a plan and the delivery of services. During the period there

must be intensive training of administrative personnel. The development of training facilities and teaching personnel is another responsibility; if it is not met by schools of public health as part of their own "get-ready" period, a chaotic educational effort will result. A far-reaching program of education is needed. Conference with the medical profession, hospitals, and potential recipients can prevent misunderstanding and throw light on the applicability of regulations.

Probably EMIC's most outstanding contribution to health administration is in attention to hospital costs and hospital standards. All of the state health departments have gained at least some experience which should be valuable in administration of P.L. 725. Under this law federal funds may be granted for hospital construction; combined federal and state expenditures for hospital and health center construction may approximate $1,000,000,000 in 5 years. The state must designate a single agency to plan and carry out the program, and minimum hospital standards must be adopted. Thus health departments which would remain aloof from the issues of medical and hospital administration, including standards and costs, should not be named as the "single state agency."

EMIC demonstrated also the complexities of the subject of medical specialization. At first glance, the administrator is responsible for preparing and publishing a list of those qualified, and the list is expected to be a duplicate of the names approved by American Specialty Boards. The medical profession, however, charged that this is an encroachment on their prerogatives. In EMIC realities appeared when state agencies accepting the medical profession's declaration placed responsibilities of designation upon the profession in the states and local areas. In EMIC specialists received a fee 50 per cent higher than non-specialists for the same service. But in the same community there may be a specialist approved by a Specialty Board, another not approved but specializing, and a third not approved but specializing to the extent of 50 per cent of his practice. Are all to be approved? And if so, what standards should replace the American Specialty Boards?

In a state where central administration by the Children's Bureau is severely denounced, it is not unusual to hear local administrators make the same criticism of state central administration. The administrative problems would be no less acute if such a program were limited to a state. The problem of fees, disregarding geographic areas or physicians' qualifications, or considering these 2 factors, thus remains the same, as does the question of specialization. This is presented not to defend a federal program but to demonstrate the complexity of the problems.

The question of whether dependence should be placed on education or regulation is best answered by "both." Regulation is necessary for the improvement of facilities. Improved services in a continuing program must be based on sound public and professional education.

The outlook of public health administrators will determine the value of the administrative lessons from EMIC. New laws on disability compensation, with related medical services, and other state and national programs bring the question of how much responsibility state health departments will assume. If a multiplicity of agencies is to be avoided, positive steps must be taken to prevent it.

MISCELLANEOUS

THE MANAGEMENT OF OBSTETRIC EMERGENCIES

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As many obstetric emergencies involve hemorrhage, shock and transfusion, and as time is important then, the Rh status of every pregnant woman should be determined early. Blood tests for hemoglobin content, Rh factor, and Wassermann reaction should done the first time she presents herself for prenatal care. If the patient is Rh negative, an Rh negative donor in the proper group must be found and the name of the donor put on her record. When a patient goes into labor, plasma should be on hand to combat shock and hemorrhage while blood is being obtained for transfusion.

Nine obstetrical emergencies are reviewed.

Placenta previa occurs in at least 1 in 300 obstetric patients. When the placenta is implanted in the region of the internal os, partial detachment with hemorrhage, appearing initially at or before the onset of labor, results from the tissue realignment incident to formation of the lower uterine segment, and the possibility of fatal hemorrhage must always be considered. Thus, (1) a patient with suspected placenta previa should be immediately hospitalized, (2) her blood should be typed and cross-matched, and (3) a donor should be selected and ready for immediate blood transfusion.

Cystography in the diagnosis of placenta previa was introduced in 1934 by Ude, Weum, and Urner, who outlined the soft tissue space between the fetal presenting part and bladder by filling the latter with an opaque medium. The technique used is as follows:

1. Empty bladder with a catheter.

2. Introduce 40 cc. of sodium iodide solution into bladder, clamp catheter.

3. Anteroposterior film with tube centered on bladder and table tilted, feet down 10 degrees from horizontal.

4. Unclamp catheter, allow bladder to drain. Remove catheter.

The interpretation of the x-ray in vertex position may be difficult and in breech and transverse presentations virtually impossible. Dippel and Brown reported visualization of placenta with a single film in about 90 per cent of 200 women by a soft tissue technique. This method requires experience; it represents an advance in diagnosis but for accuracy cannot displace sterile vaginal examinations. The only absolute diagnosis of placenta previa is digital palpation of the placenta through the cervical os.

Digital examination should not be performed till the delivery room is completely set up for emergency, since palpation of the placenta occasionally pro-

duces more bleeding. Delivery is mandatory after repeated bleeding. If the fetus is viable, a cesarean section should be performed on all cases of complete placenta previa. If the placenta previa is marginal or incomplete, or if the fetus is not viable, vaginal delivery may be employed by (1) spontaneous labor with or without rupture of membranes (may be by medical means and artificial rupture of membranes); (2) scalp traction, to which the author has never resorted; (3) a hydrostatic bag; (4) Braxton Hicks version, which should never be attempted before full cervical dilatation. All these except the first increase the fetal hazard.

Premature separation of the normally implanted placenta (ablatio or abruptio placentae), reported in 1:100 to 1:500 cases, refers to the separation of all or part of the normally implanted placenta occurring after the 28th week of gestation and prior to the onset of the third stage of labor. A moderate amount of vaginal bleeding usually associated with pain indicates partial separation. If the implantation is on the anterior uterine wall, there is frequently a circumscribed area of tenderness. Sterile vaginal examination excludes placenta previa.

Preparation for transfusion must be made even with mild vaginal bleeding, even though transfusion is subsequently unnecessary. Minimal bleeding requires little or no treatment. When bleeding is at a rate demanding delivery for hemostasis, the method depends on the condition of the cervix. With an uneffaced, firm and tightly closed cervix, cesarean section is mandatory. With cervical effacement and partial dilatation, artificial rupture of the membranes institutes labor and the bleeding is controlled by the contracting uterus. If necessary, small doses of pitocin (never more than 1 minim initially) may be given with relative safety. If these measures do not control the bleeding, insertion of a Voorhees bag to produce compression on a possible low-lying placenta, and the occasional employment of an abdominal binder, to raise intrauterine pressure to the level of blood pressure, may help.

Uteroplacental apoplexy or the Courvelaire uterus is rarely encountered. Retroplacental hemorrhage is sudden, extensive and forceful, producing acute symptoms of profound shock, and a boardlike uterus not simulated by any other condition. Immediate cesarean section is the treatment of choice, despite known presence of a dead baby, for in this condition blood infiltrates directly into the uterine muscle, dissociates the muscle fibers and inhibits uterine contractility. If the uterus will not respond to oxytocics, a hysterectomy must be done.

Postpartum hemorrhage is assuming a relatively more important role as the toxemias and puerperal infections are brought under control. Preparedness and prompt institution of treatment can all but eliminate this, one of the most frequent causes of maternal mortality. All obstetric patients should be routinely blood-typed prenatally. Special precautions should be taken if the patient is Rh negative.

Prolapsed cord in vertex presentation is usually an indication for immediate delivery, if the child is alive and the cervix dilated enough (6–7 cm. in multigravidae, 8–9 cm. in primigravidae). With lesser dilatation, hasty extraction

usually leads to severe cervical lacerations and seldom results in a living child. Delivery may be by forceps if the head is at midplane or below, by podalic version and extraction with higher stations.

If proper dilatation has not been obtained, the patient should be placed in a deep Trendelenburg position and closely watched until cervical dilatation is sufficient for the necessary maneuvers. Replacement of the cord through a partially dilated cervix is almost universally unsuccessful, and should not be attempted. Prophylactic doses of penicillin or a sulfa drug should be given to prevent ascending infection.

Prolapse of the cord occurs once in about 150 deliveries. Its occurrence depends on the presence of an excessively long cord, inadequate filling of the pelvic basin by the presenting part, and ruptured amniotic sac.

Tetanic contraction of the uterus is a possible sequel to the administration of pituitary extract, even 1-minim doses sometimes producing contractions as long as 5 minutes, or may result from other factors including long or obstructed labors. Dangers are rupture of the uterus and asphyxia of the child. The time-honored remedy is ether anesthesia. Since magnesium ions have a relaxing effect, intramuscular administration of 2 cc. of a 50 per cent aqueous solution of magnesium sulfate may help.

Bandl's ring or contraction ring is a rare occurrence: the pathological constriction about the child of the physiological ring of muscle separating the upper active contractile segment and the lower passive segment of the uterus. A spastic stricture of uterine muscle is produced. Diagnosis is made by internal palpation. The ring will probably not disappear but may be sufficiently relaxed to permit delivery following intravenous injection of 5 minims of 1:1000 epinephrine solution, or by deep ether anesthesia.

Uterine rupture, which occurs once in 2000 or 3000 cases and may be incomplete or complete, is included because fetal mortality approaches 100 per cent and the maternal risk is considerable.

Etiological factors include previous cesarean section, previous cervical operation or repair, and obstructed labor with overdistended uterine segment and operative procedures, especially internal version. Diagnosis is based upon sudden, acute and lancinating pain, with abrupt cessation of uterine pain and cessation of labor, and the rapid development of hemorrhage and profound shock. The rupture of a previously intact uterus may bring death within the hour unless heroic measures are applied.

Conservative treatment consists of either uterine and vaginal tamponade, or laparotomy with suture of the rent. Hysterectomy, the radical method of treatment, is much preferred and generally accepted; its advantages are numerous and the chance of recovery is best. In such emergency rapid mobilization of facilities and early administration of plasma and blood are vital. Hysterectomy may be demanded despite falling blood pressure, with plasma and blood given during operation.

Inversion of the uterus has a reported incidence of 1:740 to 1:16,000 deliveries. Attempts to expel the placenta before its separation either by pushing from above

or by pulling on the cord may be a predisposing cause, although fundamental etiology is unknown.

The symptoms are shock and hemorrhage associated with absence of the uterine body from the abdominal cavity and its presence in the vagina as a rounded tumor, the upper end of the mass constricted by the cervix. Active and long-continued therapy for shock is all-important. Immediate replacement of the inverted uterus under deep anesthesia has given unfavorable mortality rates, 10–43 per cent. Recent treatment has been to deal with the shock and to leave the inverted uterus alone for the time being, unless bleeding is such as to require a tight vaginal pack. Multiple transfusions may be required. Systemic chemotherapy should begin at once as a prophylactic measure, and local antiseptic vaginal packing applied daily. After 4–6 weeks in the hospital, the well-involuted uterus may then be restored surgically to its normal position or removed.

In conclusion, it is emphasized that emergency is a sudden condition, in which time is all-important. General practitioners must be prepared to deal with it, for by its very nature it cannot be placed in the lap of specialists.

OBSTETRICAL TRAINING IN VIENNA
ONE HUNDRED YEARS AGO

FRANK P. MURPHY

Bull. Hist. Med., 21: 335–351, (May–June) 1947

The lying-in division of the Vienna General Hospital was a cherished project of the Empress Marie Theresa, finally established in 1784, after her death, by her son. The institution was to provide care during confinement to unmarried gravidae, allowing the strictest secrecy. Partly because matrimony was then very difficult for people of the poorer classes, figures for a seven year period in the 1830's indicate 44,773 illegitimate births as against 56,394 infants born in wedlock.

Two groups of patients were admitted to the Vienna Lying-In Hospital: those who could pay for all or part of their care, and those who were completely destitute.

If a woman sought admission in the first group, she would be assigned according to her means and perhaps also her obvious social position. In first class accommodations, private rooms were isolated and guarded to provide the greatest possible seclusion, and accessible only to the physician and the necessary attendants. The patient with ample means could bring servants, bedding, linen as she chose. There were also 2 6-bed wards and several 10-bed wards, which a woman could enter, usually after the sixth month of pregnancy, and still maintain some anonymity. The patient could enter by an unobtrusive private entrance,

might remain veiled if she wished, could stay as long as she pleased, and might leave her baby for adoption or take it with her. She must pay in advance, and must write her name and address on a slip of paper which was locked away in her presence, to be returned to her on her departure or to be opened only in case of her death.

Whether illegitimately pregnant or not, the woman admitted to the free division had to be a pauper, a soldier's wife, or a gravida from some public institution. The "respectable" married woman was expected to stay at home or to go elsewhere. Free patients served for training graduate students or pupil midwives. While the patient might consult any physician or clergyman, no other visitors were permitted and not even the police could get any information about the patients.

If the baby was born shortly before the patient reached the hospital, she was admitted at once and questioned later. Street births frequently reached 100 a month. A patient was also admitted immediately if she had aborted or was about to do so. Otherwise, she could enter at the seventh month of pregnancy. She was given hospital garments for the duration of her stay, and could wear a veil if she wished. Usually the only work required was to help keep her ward clean.

After delivery, if she escaped childbed fever, the woman was transferred with her infant to the Foundling Hospital across the street. Here she received another hospital outfit, and had to nurse her own baby and one other at the breast. There was a surfeit of infants due to high maternal mortality from puerperal fever; but this was nicely canceled by the frightful mortality in the Foundling Hospital.

The Foundling Hospital, primarily for illegitimates, was clean and orderly, considering the population, but noisy. Each infant was given a pacifier—a piece of cloth in which a spoonful of bread and milk was wrapped—which might sometimes be left more or less in place for a week at a time. From 1784 to 1838 inclusive, 146,920 infants died out of 183,955 admissions.

At the end of 2 months stay the mother received a small bonus and if in good health could be placed as a wet-nurse. The infant could be installed in a country household; males were always welcomed as potential substitutions for the farmers' own sons in Imperial Army conscriptions.

In the 1840's the Lying-In Hospital had 3 divisions: the First, or Clinic for Physicians; the Second, or Clinic for Midwives; and the Pay Division. Gravidae were admitted to the First Division 4 days a week, to the Second on the other 3. There were 384 beds in these 2, and 57 in the Pay Division. Each prospective mother was to provide the swaddling clothes. The minimum requirement was a piece of ostensibly clean cloth for a cord dressing.

The First Division had 6 large wards for puerperae, with about 30 beds each, one largest ward for gravidae, and a labor ward with 14 beds for patients, plus rooms for the students, midwives and attendants. The Second Division was similar but smaller, and one set of windows there opened on a hall instead of in

·the clear. The wards were very clean and well-kept. However, open privies attached to the wards, which had iron grating in them to prevent infanticide and which were not to be used by puerperae for a week after delivery, a sewer running under the hospital, and cesspools of an adjoining military hospital concentrated their odors upon the hospital.

Ten certified midwives were employed in the Clinic for Physicians—a Chief-Midwife, present at every labor, who examined the placentae each morning to assure herself that the membranes had been expelled intact; the housekeeper in charge of the labor ward; and 4 on day duty, 4 others for nights. Each midwife, assigned in rotation to a parturient, had to remain with her patient until the end of labor, to tie the umbilical cord, to bathe and dress the baby, and to assist the mother in putting it to the breast. Three attendants and any gravidae capable of working were also on duty in each ward.

Forty-eight graduate students at a time received 8 weeks' training, half the period on day and half on night duty. They worked in pairs. Each pair had about 3 turns at keeping the "journal" of observations on each labor for 24 hours, and served as admitting officers during the same time. (Each time he served as journalist, the student tipped the housekeeper and the midwives.) After morning rounds with the Director and the Assistant, the journalists wrote the prescriptions, distributed the prepared medicines, applied leeches or vesicants, and performed venesections. They admitted the arriving gravida and examined her to determine the stage of pregnancy, the presentation, and the presence of any cephalo-pelvic disproportion. If the patient was actually in labor, her bed was screened and she was examined vaginally as often as was thought necessary until the bag of waters ruptured. Considering morning and afternoon clinic rounds, each woman was examined by at least 5 different people, and often many more, not counting examinations in the interval.

After rupture of membranes, the parturient was assigned to a pair of students and a midwife, who examined the patient when they saw fit, supported the perineum, delivered the baby, and watched for delivery of the after-birth. In a normal labor supervision was left to the journalists. In presence of any abnormality, the Assistant was notified. He took the responsibility, and could allow a student to operate, provided the latter had completed the course in operative obstetrics.

After labor was over, a student registered the name and age of the patient, the course and timing of labor, and the condition of the infant. Three hours after a normal delivery, the patient walked to her bed in the puerperal ward.

In the Clinic for Midwives, pupil-midwives, all married women over 18 and under 40 years of age, able to read and write and certified as to good character, received 5 months of instruction in principles of obstetrics and then 2 months practical training. Every labor was attended by a senior and a junior candidate, and the journal was similarly kept by pairs in turn who might examine all patients currently in labor.

The parturient was allowed to assume any position she chose, but in this Clinic

was usually delivered lying on her left side. Apparently, perineal lacerations were not repaired.

For the course in operative obstetrics, Dr. Braun provided a manikin, the hospital a female body, and the Foundling Hospital a constant supply of infant cadavers. Management of all abnormal presentations was demonstrated. Students might perform any or all obstetrical operations with the cadavers or the manikin: forceps delivery, version, perforation, decapitation, whatever else they fancied. In the Midwives' Clinic, demonstrations were made only on the manikin.

Gynecology

ENDOCRINOLOGY

ENDOCRINES IN GYNAECOLOGY

A. BOURNE

London, W.1.

The author takes this opportunity of replying to the various correspondents on the subject of endocrines in gynecology. The emphasis has been laid chiefly on the principle of receptor substances, or the specific sensitivity of the various tissues to the action of individual hormones. The idea of cell receptors in the end organs is by no means new, but it has not yet been exploited by researches which might enable us to expand our resources in treatment.

While discussing the general difficulties of hormone therapy, the author dwelt upon the paramount importance of the nervous factor in the control of the hormone system in man, and thus he agrees with Mr. Everard Williams when he draws attention (Feb. 8, p. 234) to the overriding influence of emotional disturbances acting through the nervous system in producing symptomatic effects in the various end organs.

Perhaps the best summing up of the difficulties of endocrine therapy is given by Dr. A. P. Cawadias (March 22, p. 390) when he describes the disorder not as a separate disease of one or more of the 6 chief glands but as a pathological "complex" based upon irregular function of the whole psychosomatic system, including the endocrine glands, and all in relation to environmental factors.

(As the author himself states, there is no scientific proof of "receptor substances," but there is no question as to variations in the degree of sensitivity or refractoriness of end organs to the effects of similar dosages of the hormone to which the particular tissue is specifically and characteristically responsive, as for example the genital tract and the mammary gland are specifically influenced by the ovarian hormones. I have frequently commented, in these pages, on such variations in receptivity, and given illustrative examples, suggesting that they are of innate, possibly of congenital or genetic origin. Whether this is true or whether there are variations in some hypothetical "receptor substances," such as Bourne postulates, no one can say, although one may say that the latter hypothesis would, after all, have to fall back on the first as a more underlying one.

As to the importance of the nervous factor in many endocrine disorders there would seem to be no doubt, nor is this surprising if one conceives of the whole endocrine system as representing a primitive apparatus for the intercommunication which in such highly sublimated form is the chief function of the nervous system. In this primitive "chemical messenger" intercommunication system represented by the endocrines, the pituitary represents the endocrine brain. Numerous examples can readily be adduced to illustrate that a close liaison persists between the nervous and endocrine systems.

The generalization expressed in the last paragraph of the abstract is a rather self-evident one, but the fact remains that in numerous endocrinopathies some one or other of the endocrine glands can be, on good evidence, convicted of dominating responsibility for the par-

was usually delivered lying on her left side.   Apparently, perineal lacerations were not repaired.

For the course in operative obstetrics, Dr. Braun provided a manikin, the hospital a female body, and the Foundling Hospital a constant supply of infant cadavers.   Management of all abnormal presentations was demonstrated. Students might perform any or all obstetrical operations with the cadavers or the manikin: forceps delivery, version, perforation, decapitation, whatever else they fancied.   In the Midwives' Clinic, demonstrations were made only on the manikin.

and premature fusion of the epiphyses. The evidence that female pseudohermaphroditism is due primarily to an abnormal secretion of hormones is now very convincing; the authors cite the production of freemartins in certain animals in which the placental circulation of male and female embryos may be mingled. Also, the administration of androgens during pregnancy leads to the birth of female pseudohermaphrodite offspring in experimental animals.

It has been suggested that the syndromes which occur with congenital hypertrophy and tumors of the adrenal cortex are similar in pathogenesis. In both there is abnormal hormone secretion and a tendency to virilism. However, it should be noted that in carcinoma of the adrenal cortex there is usually some degree of muscular atrophy, osteoporosis, obesity and often insulin resistant diabetes, while the andro-genital syndrome of congenital hypertrophy of the adrenal cortex is usually associated with precocious muscular and skeletal development and diabetes is rare. This distinction may possibly indicate a preponderance of different hormones in the 2 conditions.

Diagnosis and treatment are discussed. In diagnosis, the occurrence of blood loss from the vulva in the first few days of life is suggestive of the presence of a uterus. Palpable adrenals in a pseudohermaphrodite might suggest that the infant was likely to be a female. The vomiting which is frequently seen in infants with this type of adrenal hypertrophy may possibly be due to desoxycorticosterone deficiency; the evidence is at least sufficient to warrant administration of desoxycorticosterone during an attack of diarrhea and vomiting. In the few cases of congenital adrenal hypertrophy which have been subjected to operation, in comparison with adrenalectomy for tumors, the results are not encouraging. 4 figures.

(While Biggs and Rose mention certain differences in the syndromes produced by cortical hypertrophy and such cortical neoplasms as carcinoma, these are on the whole not impressive, and for practical purposes the syndromes are pretty much alike. In my comment on a paper published in a previous issue of the SURVEY, I emphasized the fact that it is in this type of pseudohermaphroditism that one finds the urethra opening into the vaginal canal a short distance within the introitus, and this was noted in several cases of my own. It is of interest to note that exactly the same anomaly was observed in the 2 cases reported by Biggs and Rose. The not infrequent familial incidence of this type of intersexuality is strongly suggestive of its probable genetic etiology, the adrenal hypertrophy being apparently the anatomic expression of the disturbed genic sex balance.—Ed.)

ETHINYL ESTRADIOL

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and D. A. Sherber

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Experience with various uses of ethinyl-estradiol, an extremely potent oral estrogen, is presented. Of 57 women suffering from both surgical and natural

ticular disorder, and corrective therapeutic measures can therefore be rationally concentrated upon this particular member of the endocrine mechanism.. If examples are necessary, one can mention the dominating notes of the adrenal in Addison's disease, the thyroid in Graves' disease, the ovary in the menopausal vasomotor syndrome, etc.—Ed.)

THE FAMILIAL INCIDENCE OF ADRENAL HYPERTROPHY AND FEMALE PSEUDOHERMAPHRODITISM

ROSEMARY BIGGS AND ELIZABETH ROSE

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The authors present 2 cases of female pseudohermaphroditism associated with adrenal hypertrophy which occurred in the same family. The affected infants were the second and third children born to normal, non-related parents. The first child is a normal female, now aged 7 years.

The second child was considered to be a female because of blood loss from the vulva during the first few days of life. There was marked hypertrophy of the clitoris and no vaginal orifice was seen. At the fourth week of life severe vomiting and weight loss commenced and persisted until death at the age of 6 weeks. The third child, born 2 years later, had gross hypertrophy of the clitoris and no vaginal orifice was seen; general opinion in regard to sex determination favored the diagnosis of a male. At 4 weeks of age, the baby died within a day from a sudden attack of vomiting.

The postmortem appearances of the 2 infants were similar. There was hypertrophy of the clitoris. The urethra and vagina had a single external orifice, but the 2 were separated by a septum reaching almost to the vulva and were actually well developed. Normal uterus and ovaries were present. The adrenals were enlarged and weighed 8 g. each. The cortex was finely convoluted, producing a great increase in the total cortical tissue. Microscopically, the clitoris contained much erectile tissue. Rudiments of prostatic glands were present at the base of the bladder and in the urethro-vaginal septum. The adrenal cortex was markedly increased in thickness and there was less than normal regularity in the general arrangement of cells. The demarcation between cortex and medulla was less sharply defined than usual. The pituitary showed an increase in the proportion of basophil cells in the anterior part.

About 100 cases of female pseudohermaphroditism have now been described. Although the defect is less clearly hereditary than is male pseudohermaphroditism, in a number of families more than one member of a generation were involved. Nine families are recorded in which 2 sisters were pseudohermaphrodites, and in 4 families both males and females were affected.

The primary defect is probably adrenal hypertrophy. An exactly similar hypertrophy of the adrenals may occur in the male, leading most commonly to enlargement of the penis, hirsutes, rapid growth, unusual muscular development

mammary substance. (5) Menstruation is primarily characterized by the usual occurrence of clots and by usually profuse flow. (6) Libido is often low or absent. (7) Pelvic findings are variable, but uncomfortable hyperesthesia and some degree of pelvic congestion or edema are usual.

The writer suggests that microscopic examination of fresh, wet saline preparations from the vagina may be helpful in evaluating the clinical picture. In treatment, the etiologic factor should obviously be eliminated. General hygiene, elimination of vaginal and cervical infections and relief of pelvic congestion by hot douches are primary therapeutic considerations.

(This paper takes one back to the days of loose, comfortable and incidentally absurd attempts to make of endocrinology a system of diagrams, showing by a complicated system of lines just what symptoms were due to hyper-this and hypo-that. A glance at the signs and symptoms which the author includes under the designation of "hyperestrinism" will suggest that the editor might have nodded just a bit in publishing this communication. Hyperestrinism is certainly not always associated with menstrual excess, but may be seen with long periods of amenorrhea. Libido, so far as I know, has nothing to do with hyperestrinism, or probably with any other form of ovarian misbehavior. The shot-like consistency of chronic mastitis is commonly seen in the entire absence of hyperestrinism, being explained by the sensitivity of some women's breasts to the growth effect of estrogen. And so on down the line. One does not have to be ultra-scientific to deplore such papers as this.—Ed.)

menopause, 79 per cent had complete relief from symptoms, 17 per cent had moderate relief, and 4 per cent obtained no relief. Vaginal smears became fully cornified in all patients in this group. Fourteen per cent of the group had nausea and vomiting, but in no instance was this severe enough to interfere with therapy. Vaginal bleeding occurred in 20 per cent, but was never severe and always stopped on cessation of therapy.

Of 24 cases of primary and secondary amenorrhea, all patients were made to bleed periodically. Growth of the uterus and cervix was accomplished in all cases. Two patients complained of mild nausea.

Ethinyl-estradiol was used to prevent breast engorgement and inhibit lactation in 145 nonnursing postpartum mothers. Results were excellent in 58 per cent, good in 16 per cent, fair in 16 per cent, and poor in 10 per cent. In 26 nursing mothers to whom ethinyl-estradiol was given, there was no suppression of lactation or engorgement in 6 patients, partial suppression of lactation and engorgement in 17 patients, and complete suppression of lactation and engorgement in 6 patients.

The use of ethinyl-estradiol in the induction and hastening of labor is presented.

(The purpose of this paper is obviously to show that ethinyl estradiol is a potent estrogenic substance, which would be conceded by everyone who has had experience with it; just as there would be similar agreement as to the estrogenic potency of many other available preparations, such as diethylstilbestrol, hexesterol, premarin, dienestrol, meprane, theelin, amniotin, etc. These substances of course vary in their degree of potency, their degree of toxicity, and also their expense to the patient. The average gynecologist will be likely to have his favorites among them, but he should be sufficiently versatile to adapt his estrogens to the particular patient's indication. For example, not infrequently one prefers a preparation of comparatively low potency to one of the more high-powered variety.—Ed.)

HYPERESTRINISM IN PRIVATE PRACTICE

R. T. SPICER

Miami, Fla.

It is the purpose of this paper to present a hyperestrin syndrome. If there is such a clear-cut picture as a clinically obvious hyperestrin syndrome, its recognition will stop the abuse of estrogens and will indicate a rational approach to the alleviation of refractory complaints which are too often treated with estrogens.

From a review of records made in private practice the writer offers for consideration the following symptoms and signs under a classification of "hyperestrin syndrome": (1) Premenstrual nervous and emotional irritability. (2) Premenstrual or menstrual headache. (3) "Allergic rhinitis." (4) Premenstrual hypersensitiveness of the breasts, plus a "shotlike" or nodular consistency of the

in the fundus is slow to contract and even slower to relax. These different pressures allow organized contractions to propel menstrual debris downward and out of the cervical canal. Disorganized contractions or the development of a contraction ring, as observed in one patient, may interfere with this milking action causing undue distention and pain in certain instances.

The writers conclude that dysmenorrheic patients fall into loosely defined groups, some of whom are more or less true types with high pressure uterine contractions quite regular and accompanied by high intercontraction tones. These patients respond well to spasmolytics. However, in many others there must be a multiplicity of factors besides the myometrial, all of which together produce the symptom complex. A tentative outline of the other factors contributing to dysmenorrhea is presented. 5 figures.

(We poor clinicians are likely to be pretty confused by the diversity of opinions, based on physiological studies which each author no doubt considers impeccable, as to the normal hormonal control of the uterine contractility, as well as the behavior of the uterine muscle in cases of dysmenorrhea. I have talked with quite a number of the workers in this field, and it is rather amusing that most of them explain the other fellow's contradictory results by a kindly criticism of the method of study he employed. I am sure that I am qualified to evaluate either the methods or the results, and this certainly applies to the study abstracted above. But I am still confused about the subject just the same.—Ed.)

DYSMENORRHEA AND OVULATION: CORRELATION OF THE EFFECT OF ESTROGEN THERAPY ON PAIN, THE ENDOMETRIUM, AND THE BASAL BODY TEMPERATURE

L. W. Haus, J. W. Goldzieher and E. C. Hamblen

Duke University School of Medicine and Duke Hospital, Durham, N. C.

Fifty-four patients were studied by the authors for a total of 228 cycles. Eighty-two biopsies and 11 basal temperature records were obtained. All anovulatory cycles were pain-free. All ovulatory cycles were accompanied by pain except one in which an early progestational endometrium was associated with no pain.

One of the most striking characteristics of functional dysmenorrhea is its invariable correlation with a progestational endometrium or an ovulatory type of basal temperature curve. On this basis it has been concluded that ovulation is a prerequisite for dysmenorrhea, and treatment has been aimed at the suppression of ovulation. Thirty-three patients were treated with a total dose of less than 25 mg. of premarin or less than 20 mg. of diethylstilbestrol. Of these 12, or 36.4 per cent, obtained total relief of pain. Of 17 patients treated with 25 mg. of premarin or with 20 mg. of diethylstilbestrol, 8, or 47 per cent, obtained total relief. Of 11 patients treated with 50 to 75 mg. of premarin or with 40 to 60 mg. of diethylstilbestrol, 8, or 72.7 per cent, obtained total relief.

THE MENSTRUAL CYCLE

THE NATURE OF DYSMENORRHEA

R. TORPIN, R. A. WOODBURY AND G. P. CHILD

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The writers discuss the need for developing objective methods to evaluate the degree of dysmenorrhea and its alleviation, methods which lead to the study of the uterus itself and its adjacent and component parts.

Using the Hamilton optical manometer and very small single or multiple balloons inserted into the uterus, and with needles inserted into blood vessels, pressure changes may be recorded simultaneously, showing all changes to within 1/200 second. This permits determination of exact intercontraction tone pressures and also permits exact measurements of the amount of distention of the uterine cavity. The balloons serve as foreign bodies resembling the menstrual debris. The uterus responds to this load of the distended balloon by attempting to expel it, but gauze packed against the cervix prevents this.

Pressure curves show that organized and disorganized contractions and a mixture of these types occur. The disorganized or mixed type was observed more frequently in the patients having dysmenorrhea, while the organized type was observed more commonly in the control patients. Yet, no particular type of tracing is always associated with dysmenorrhea.

In patients in whom menstrual pain is intermittent in nature, low uterine pressures were present between contractions. Patients who developed steady severe low abdominal cramps generally showed uterine contractions with high intercontraction tone. However, an occasional patient does suffer severe pain even with pressures associated with contractions possessing low amplitude and low tone. The observation that pain can be associated with uterine pressures of only 10 to 15 mm. Hg differs from all of the previous reports.

Two impressive and revolutionary observations were that the characteristic pain could be produced in all of the 25 patients by the injection of pitressin or by stretching of the uterus by increasing the fluid in the balloon. Pitocin, histamine, and acetylcholine cause less increase in uterine activity than that caused by pitressin; also the contractions tend to remain better organized. Nulliparous patients as a group accommodate less distention of the balloon than was tolerated by parous patients. Bearing a child apparently increases the tolerance of the uterus to stretch by enlarging the uterus. This may account for the relief of menstrual distress after bearing the first child in some patients.

Records were obtained simultaneously from 3 balloons inserted at different levels in the uterus and from one balloon inserted into the cervix. The cervical contractions are generally shorter and more frequent, whereas the musculature

be suspected—even without any evidence of pelvic pathology on bimanual palpation. This will occur in about one out of 60 cases of dysmenorrhea, and these patients should be immediately transferred from estrogenic therapy to testosterone, 25 mg. hypodermically, twice a week for 3 months. After this period of time the pessary can be removed and the testosterone given 25 mg. hypodermically about 5 to 10 days before each period. This will so modify estrogenic action that hypertrophy of the endometrial implants is inhibited and in the author's experience, no masculinizing effects are noticeable and pregnancy can still occur. This routine gives an excellent opportunity for early cases of endometriosis to be detected and controlled before extensive pelvic alterations occur, and will decrease the necessity for surgical interference.

(This paper certainly does not "ring the bell" as far as I am concerned. I would certainly not wish to depend upon such hormonal tests as the author recommends to make the diagnosis. Nor do I believe that one should often assume the presence of endometriosis in the complete absence of any such palpable findings as an enlarged adherent ovary or nodules in the uterosacral ligament just because the patient has dysmenorrhea, regardless of the reaction to hormones. I am afraid that such an assumption is fairly common, and endometriosis is all too often not found at operation. When the pelvic organs seem entirely normal under satisfactory palpation, the dysmenorrhea is far more frequently of the common primary type. It is quite true that in such cases there may be small "implants" on the ovary or elsewhere, but it is doubtful whether these have anything to do with the dysmenorrhea. Certainly they are not infrequent accidental findings in women who have little or no menstrual pain.

As to the hormonal treatment of primary dysmenorrhea, it is quite true that fairly large estrogenic dosage begun very early in the cycle, in my own practice about the second day, and kept up for approximately 12 days, will often make the next period relatively painless through the inhibition of ovulation thus produced, though proper oral therapy is just as effective and far more agreeable to the patient than the daily hypodermics recommended by the author. A repetition of the plan during the next cycle is apt to give less satisfactory results, so that the plan should be used only intermittently, especially as too long continuance may cause disturbance of menstrual rhythm. Nor would too frequent resort to this hormonal inhibition of ovulation be desirable in dysmenorrheic young married women anxious for children. As to the use of stem pessaries for dysmenorrhea, I have commented briefly upon this in connection with another abstract in this issue.—Ed.)

A STUDY OF CERVICAL CULTURES TAKEN IN CASES OF ACUTE GONORRHEA WITH SPECIAL REFERENCE TO THE PHASES OF THE MENSTRUAL CYCLE

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It is concluded that there is a definite correlation between the isolation of the gonococcus from cervical cultures and the phase of the menstrual cycle in which the cultures are taken.

Of 91 cycles treated with less than 25 mg. of premarin or with less than 20 mg. of diethylstilbestrol, 23, or 25.3 per cent, were totally pain-free. Of 53 cycles treated with a total dose of 25 mg. of premarin or with 20 mg. of diethylstilbestrol, 26, or 49.1 per cent, were totally pain-free. Of 23 cycles treated with 75 mg. of premarin or with 60 mg. of diethylstilbestrol, 18, or 78.3 per cent, were totally pain-free. It is obvious that the chances of obtaining relief in any cycle or in any individual patient increase as the dose of estrogen is increased. In order to establish the optimal dosage for the individual patient, it is advisable to follow treatment with endometrial biopsies or with basal temperature records.

No gross menstrual disturbances followed the described dosage schedule of estrogen administration, although the dosage of some patients was relatively large.

The presence either of progesterone or of its physiologic effects is a prerequisite for dysmenorrhea. Although it is initiated by progesterone, other details of the pathogenesis of dysmenorrhea are unknown. 3 figures.

(It may still be premature to be dogmatic on the subject, but the evidence does seem quite overwhelming that it is the ovulating women who have the primary dysmenorrhea, while anovulatory cycles are characteristically painless. The present authors add further evidence on this point. As a matter of fact, the mere fact that a woman has typical primary dysmenorrhea is pretty good *prima facie* evidence that she is ovulating, and this would almost eliminate the necessity for ovulation tests, such as endometrial biopsy or basal temperature records, in the study of sterility in such women. The quantitative clinical study made by the authors confirms the impression that to suppress ovulation and give relief from the pain of the succeeding cycle, fairly large estrogen dosage in the preovulatory stage is necessary.—Ed.)

A DISCUSSION OF THE TREATMENT OF FUNCTIONAL DYSMENORRHEA AND A HORMONAL TEST FOR ENDOMETRIOSIS

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Dysmenorrhea is a symptom complex of several disorders from which potential cases of endometriosis must be diagnosed early. After pelvic examination, every severe dysmenorrhea associated with no gross pathology, after the age of 20 should be treated first by hormonal therapy of about 50,000 units of estrin or estradiol hypodermically in the first 2 weeks postmenstrually, combined with the insertion of a stem pessary. Treatment should be continued for about 6 months before removing the pessary. After 2 to 3 months' treatment, in most cases dysmenorrhea will disappear. If, over a 3-month period, dysmenorrhea increases instead of disappearing, the presence of internal or external endometriosis should

VULVA AND VAGINA

MELANOSARCOMA OF THE VULVA

FRIEDERICH TEUFELMAYR

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Mrs. L. v P. was admitted to the Women's hospital at Linz, Austria, suffering from a swelling on the vulva. Her family history was good and she had been in excellent health until 1934, when sugar was found in her urine and she underwent insulin treatment for 4 years. She had had no difficulties during the climacteric period and had borne 3 children.

Early in 1942 the patient noticed several pustules on the labia majora accompanied by a swelling of the vulva and pains which disappeared within a month.

In the spring of 1943 the ailment returned, disappearing within 2 weeks, but shortly thereafter she noticed 2 small black spots on the left labium minus, followed by the appearance of a hard lump on the right labium, similar to a small mulberry in size and color. After several weeks it had increased in size and had begun to bleed on the surface. On July 20th she developed cardiac symptoms with highly accelerated and highly sensitive cardiac action, followed by loss of appetite and intolerance of many foods.

An examination of her condition upon admission to the hospital some weeks later showed the skin of the breasts, back and abdomen to be thickly strewn with pigmented nevi somewhat larger than lentils. On the right labium was a hard blue lump the size of a hazelnut, of brownish-black color, embedded in a strongly pigmented grayish-black area. The internal genitalia were normal. In the right and left groin there was felt a chain of enlarged but not painful glands.

Vulvectomy with radical gland extirpation was done in 2 stages, followed by deep x-ray therapy. The last report on March 21, 1943 showed recurrence of extensive pigmentation in the vulvar region. The patient presumably succumbed to her disease. Histological examination revealed a typical melanosarcoma.

Melanomas of the vulva are extremely interesting to the gynecologist not only because of their histological character but also because of their rarity. While some classify them as sarcomas and therefore speak of them as melanosarcomas or melano-plastic sarcomas, others call them carcinomas.

Such tumors may be found almost anywhere on the cutaneous surface of the body, usually emanating from a pigmented nevus. Their malignancy is the same in all locations, likewise their tendency to cause general metastasis. Most result in a fatal ending within 18 months. In the female genital organs they are most frequently found on the large and small labia, where skin irritation through secretions from the vagina, the friction of the clothing, and manipulation of the

In a total of 128 cervical cultures, 69.4 per cent, or 89 cultures, were positive; of these, 94.2 per cent, or 84 cultures, were positive during the estrogenic phases and the early part of the luteal phase of the cycle when the pH of the cervical mucus was 6.8 and above. Thirty-nine cultures, or 30.6 per cent, were negative. Of these, 26, or 66.4 per cent, were obtained during the latter part of the luteal phase when the pH range was 6.4 to 5.2.

Apparently several consecutive negative cultures without the knowledge of the pH of the cervical mucus at the time of culturing do not mean absence of infection. Acid mucus is associated with negative cultures when there still may be active foci of infection, possibly deep in the cervical glands.

An investigation of the effect of low pH upon the viability of the gonococcus was tested in vitro. Pancreatic digest broth adjusted to various pH values was used as the test medium. Six freshly isolated strains reacted in the same manner. When grown in broth at pH 6.8, growth was reduced approximately 50 per cent, as evidenced by colony counts, in comparison with growth in broth at pH 7.2. At pH 6.4 and 6.0 the organism remained viable for 4 and 2 hours, respectively.

Pure crystalline progesterone incorporated in pancreatic digest broth giving a final concentration of 1 to 20,000 completely inhibited the growth of the gonococcus in 2 hours, regardless of the pH of the medium.

The writer concludes that whenever possible the pH of the cervical mucus should be tested at the time of culturing. When this is not possible, the date of the onset of the patient's last menstrual period should be noted when the cultures are taken.

(The ideas expressed by the author seem sensible, and are apparently substantiated by the much higher proportion of positive cultures obtained in the estrogenic and early luteal phases as compared with the late luteal.—Ed.)

MYCOTIC VULVOVAGINITIS AND THE VAGINAL FUNGI; A REPORT OF 280 PATIENTS

C. P. Jones, B. Carter, W. L. Thomas, R. A. Ross and R. N. Creadick

Duke University School of Medicine and Duke Hospital, Durham, N. C.

This report deals with a group of 280 selected patients, both pregnant and nonpregnant, who sought medical advice because of pruritus vulvae and other symptoms referable to a mycotic vulvovaginal infection. No patient with complicating diseases was included. There were 189 nonpregnant patients and 91 pregnant patients. All of the patients except 3 were in the menstruating age. Two patients were between 50 and 60 years old, and one patient was over 60.

Candida albicans was isolated and identified from 91.07 per cent of these patients. Other species of *Candida* were responsible for vulvovaginitis in the occasional patient.

The writers conclude that fungi belonging to the genus *Candida* are etiologic agents in a specific form of vulvovaginitis. Although the disease is more frequently recognized, many patients do not show signs, and the diagnosis is not made because of the failure to use culture methods.

The pathogenicity of certain of the vaginal fungi belonging to the genus *Candida* has been proved. Reports on the production of symptoms by the experimental inoculation of the vagina with pure cultures has been uniformly successful. However, the mechanism whereby symptoms are produced in some patients but remain absent in other patients who carry in the vagina the same species of *Candida* is still not understood.

The primary complaint is *pruritus vulvae*. Other complaints which are secondary to the pruritus are irritation of the vulva and introitus with dyspareunia. Increased discharge is nearly always preceded by pruritus. The most helpful physical finding is the presence of a white, flaky or cheesy vaginal discharge. This discharge should be collected for microscopic examination and culture. Vaginal and vulvar findings vary from apparently normal to a diffuse hyperemia of the vagina, cervix and vulvar areas.

As to treatment, it is the writers' opinion that x-ray is contraindicated in all types of vulvar disease. The application of 1 per cent aqueous gentian violet is messy, and chemical reactions are not uncommon. For the past 2 years the authors have been using a vaginal jelly with a bentonite base and calcium and sodium propionate as the active ingredients. Over 100 patients have been treated with excellent results. A cure was obtained after one series of treatments in 80 per cent of the nonpregnant patients and in 33 per cent of the pregnant patients. Even though cultural cures were not effected in many pregnant patients, symptomatic relief was obtained. 1 figure.

(The report by the authors of 280 patients with mycotic vulvovaginal infection would at once suggest that it must be far more common than the average gynecologist suspects.

genitals are contributing causes. Trauma is frequently cited as another cause, likewise leucorrhea and parturition. Nevertheless many cases of melanosarcoma have been discovered among women who have never given birth to a child or suffered from chronic irritations or trauma. Eighty per cent of the recorded cases were among women over 40.

Virchow divides the melanotic tumors into 3 classes: simple melanomas, melanocarcinomas and melanosarcomas, but these definitions are purely arbitrary. Some pathologists believe them to be of epithelial origin while others attribute their formation to a sarcomatous degeneration of elements in the connective tissue.

Pigmented nevi play a role not yet fully explained in the formation of melanotic tumors. Certain it is that melanomas on the cutaneous surface often develop from such nevi. It is nevertheless noteworthy that although pigmented nevi are exceedingly numerous in the human body, the number of melanomas is relatively very small.

The symptoms are unfortunately most uncharacteristic in the early stages of the disease. Patients often visit the physician because of harmless appearing ailments such as itching and burning in the genital regions, or slight bleeding from superficial ulceration, during coitus or upon washing the genitals. If the tumor is near the urethra there are urinary disorders. Sometimes treatment is sought because of pains resulting from swollen glands in the inguinal region. In such cases the tumor is often well developed and metastasis has already begun.

Metastases may appear almost anywhere. According to Kotzaroff the sites preferred are of mesodermal origin. The course of the disease is not more than 18 months or 2 years. A permanent cure is exceedingly rare, and even in cases where considerable time has elapsed since the operation there is usually a recurrence in the form of a general metastasis.

The diagnosis of a melanosarcoma is simple, because of its characteristic pigmentation. Exploratory excisions should be made with extreme caution because of the danger of spreading the infection. The presence of melanin in the urine serves as a confirmation of the diagnosis in cases where therapeutic intervention is useless because of an already existent metastasis.

In the absence of metastasis most writers agree that surgical intervention of the most radical character is indicated in melanosarcoma of the vulva. The removal of the vulva, together with the superficial and deep-seated glands, followed by x-ray treatment is indispensable. A non-radical operation serves merely to promote its further growth. It remains to be proved, however, whether the procedure indicated above will produce better results in the treatment of melanosarcoma.

(There has been much discussion among pathologists as to the histogenesis and nomenclature of this very malignant tumor type, which fortunately is only rarely encountered in gynecological practice. Instead of calling them melanosarcoma or melanocarcinoma, many now use the designation of melanoma, chiefly because of the fact that the studies of Masson in 1932 apparently established the derivation of these tumors from the modified Schwann cells of the peripheral nerves.—Ed.)

be improved upon, except in the case of the "transverse vaginal sulcus", which Surti believes should be called "urethro-vesical sulcus." The terms "transverse" and "vaginal" are both superfluous because all the grooves described by Mr. Shaw, except the "oblique vaginal folds", are transverse and all are situated on the anterior vaginal wall.

In the description of vaginal hysterectomy for severe degrees of uterine prolapse, Surti feels that the name of A. C. Palmer has been inadvertently omitted. The technique devised by Palmer, though similar to that of Mayo and Franz, is not quite identical with it, and lays emphasis on certain features which merit mention of his name.

Most of us, I feel quite sure, make such a diagnosis only occasionally in private practice. This is no doubt due, as the authors suggest, to the fact that so many patients do not present any actual local signs, the pruritus being the important and often the only symptom. It is only by such routine cultural methods as the authors employed in their clinic that one could hope to demonstrate the incidence of infection with this fungous parasite, which the authors prefer to speak of as the *candida*.

The time-honored treatment of this type of vulvovaginal infection has been the employment of a 1 per cent aqueous solution of gentian violet, and the results reported have been in the main been satisfactory, though probably less so than those observed by the authors from the use of the vaginal jelly which they recommend.—Ed.)

GYNECOLOGY: THE VAGINAL SMEAR

H. Ulfelder and J. V. Meigs

Boston

New England J. Med., 237: 54–56, 1947

The vaginal smear is a simple, painless and universally applicable method of observing and recording certain changes in the status of the female internal genitalia. Degrees of estrogenic effect can be distinguished in the vaginal smear, and by means of day-to-day smears, an experienced observer can also occasionally draw conclusions regarding corpus-luteum function.

In cancer of the genital tract, the smear is of help not only in diagnosis but also in prognosis and in the detection of persistent or recurrent disease.

(The vaginal smear is of unquestionable value in evaluating estrogenic effects, of far less value as a measure of progesterone effects. As to its value in the diagnosis of genital cancer, numerous editorial evaluations of this procedure have been expressed in previous numbers of the Survey. Suffice it to say here again, that it is not intended, even by its chief champions, to replace the more decisive procedure of biopsy in the diagnosis of cancer, that in most cases it is to be looked upon as a supplementary procedure, and that, on the basis of available evidence, its most promising and certainly most rational indication is as a screening procedure in the examination of ostensibly normal women.—Ed.)

SURGICAL ANATOMY OF THE VAGINA

B. S. Surti

London, W. C. 1.

Brit. M. J., 1: 655, 1947

It is stated that students of gynecology will be extremely grateful to Mr. Wilfred Shaw (April 12, p. 477) for having described the surgical anatomy and operations of the vagina in lucid and masterly style. The terminology cannot

should be made and a specimen of tissue removed for examination. If the lesion is operable, the writer advises to proceed with the major operation at once. Patients having involvement of the uterine body and for whom the surgical risk is good are usually treated by total abdominal hysterectomy plus removal of the tubes and ovaries; when the disease has spread to other organs or regional lymph nodes are enlarged a more radical procedure, followed by roentgen ray therapy, is considered.

Treatment of epithelioma of the cervix is much more difficult than treatment of carcinoma of the body of the uterus. After discovery of the beneficial effect of treatment of local growths with radium and roentgen rays, radiotherapy was, with few exceptions, advised for all cases of epithelioma of the cervix. After a sufficient number of patients was thus treated, it was found that, while the local lesion was apparently eradicated, all but about 25 per cent of the patients died of carcinoma and many of those living had complications from radiotherapy. In recent years many gynecologists have advised a Wertheim type of hysterectomy, either preceded or followed by roentgen ray therapy, in all cases of early malignant disease of the uterus in which the surgical risk was good. The results are that a large number of 5-year cures has been secured and practically no postoperative complications have occurred.

If surgical removal is indicated, it is recommended that it be done by a surgeon familiar with the Wertheim type of operation, and that it be completed in $1\frac{1}{2}$ hours. If radiotherapy is indicated, it should be given by specialists in such treatment. Preoperative preparation, including care of the vagina and the local growth, careful thorough dissection of the regional lymph nodes, chemotherapy, modern anesthesia given by an expert and recognized anesthetist, and modern postoperative treatment are all essential. 3 figures.

(The author, a gynecologist of very large experience, lays greater stress on the histological gradation of both cervical and corporeal cancer than do most gynecologists and radiologists of the present day. The greater malignancy of the unripe varieties as well as their greater radiosensitivity, appear to be borne out in general, and yet many radiologists of great experience have found such individual variability in response, entirely apart from cell type, that they pay much less attention to the latter than they did formerly. The clinical stage of the disease is a more important factor in determining the fate of the patient than is the histological gradation of the tumor. On the other hand, the observed response of the lesion to radiotherapy is often a factor of much importance in deciding on the advisability or inadvisability of radical operation in otherwise suitable cases.

The author states that 41.7 per cent of traced patients with cervical cancer were cured by surgery, but this figure means little unless the series is broken down into the various clinical stages. It would be rather low if it referred to the early cases of Stage 1, very high if it has reference to all clinical stages (one should not confuse clinical stages with histological grades). However, no one would select advanced stages for operation, so that I presume that the author's figure referred to Stage 1 and probably some of those of Stage 2.

In discussing corpus cancer, no mention is made of operation preceded by irradiation, though this is the plan advocated by most gynecologists at the moment, with of course some exceptions on the basis of individual indications.

The author's admonition that the Wertheim operation, including lymph gland dissection, should be done only by surgeons thoroughly familiar with the technique is a wise one, but one which I am afraid is being violated nowadays by some who have been influenced by the

THE UTERUS

CARCINOMA OF THE UTERUS

J. C. Masson

Mayo Clinic

Surg. Clin. North America, 27: 763–774, 1947

The only hope for cure of carcinoma of the uterus lies in early diagnosis and early institution of modern methods of treatment.

In a broad evaluation of carcinoma, one of the most important considerations is the degree of malignancy of the individual tumor, as suggested by Broders. By his method, the most malignant growths, in which marked departure from the normal cell structure and arrangement occurs, are classed as "grade 4," whereas the least malignant tumors, in which there is little change from the normal cell structure and arrangement, are classed as "grade 1." At the Clinic, from 1910 to 1944 inclusive, 1,694 cases of corpus carcinoma were distributed, by grade of malignancy (Broders), as follows: grade 1, 34.2 per cent; grade 2, 38.4 per cent; grade 3, 13.1 per cent; and grade 4, 14.3 per cent. During the same time, 3,962 cases of cervical carcinoma were distributed as follows: grade 1, 2.5 per cent; grade 2, 14.8 per cent; grade 3, 47.2 per cent; and grade 4, 35.5 per cent.

The classification of Schmitz, which takes into account the amount of local involvement, is considered by the author to be a useful, but by no means accurate, method of tabulating cases. The grade or type of malignancy is more important than the extent or location of the primary growth.

Experience has shown that the less the differentiation, the greater the resistance to radiotherapy. For tumors which are resistant to radiotherapy, radical surgical removal gives the best results. Highly malignant tumors, however, with marked cellular differentiation, respond more favorably, in many cases, to treatment with radiotherapy and, except at a very early stage, are difficult to cure by surgery alone. While 41.7 per cent of traced patients who had malignant lesions of the cervix (all grades) were cured by surgical removal with or without radiotherapy, only 29.4 per cent were cured by radiotherapy alone. The corresponding figures for corpus carcinoma were 68.7 per cent and 21.3 per cent. However, these incidences do not give a true guide as to the merits of surgery and radiotherapy, since the condition of many patients who were treated with radiotherapy alone was considered inoperable and only palliation was attempted.

Three types of treatment are recognized: (1) surgical removal of the local growth plus removal of regional lymph nodes, (2) application of radium to the local growth plus administration of roentgen rays over the pelvis, and (3) surgical removal plus radiotherapy. Following a thorough medical check and efficient, preoperative preparation, an examination, with the patient under anesthesia,

69.2 per cent 5-year survival rate; stage 2, 60.2 per cent; stage 3, 29.7 per cent; and stage 4, 6.5 per cent. These results concerned patients treated primarily at the Clinic. In a group of "modified" cases, in which the patients received treatment elsewhere before coming to the Clinic, the results were not so satisfactory. The 5-year survival rate of all patients, primary and modified, in all stages, was 26.8 per cent of 1,352 patients traced.

It must be remembered that palliation gained by limited treatment is often invaluable and many patients who have massive cancers must not be refused a chance of help, even though the 5-year survival rate is greatly lowered by accepting such patients.

The chief complications encountered during the first course of treatment in 5 or 6 per cent of the Clinic's patients have been due to spread of infection or to hemorrhage. All cervical cancers are infected when first seen. Of late years, topical application of sulfonamide powders during treatment has appeared to cut down the spread of infection. However, when pelvic cellulitis spreads, eventuating in a pelvic abscess or peritonitis, cancer therapy is stopped and measures are taken against infection. Cancer therapy is resumed when the infectious spread has been halted and the patient's temperature returned to normal. Hemorrhage associated with cervical carcinoma is treated by tight packing of the vagina with gauze every other day while proceeding with radium therapy. After several radium treatments a few days apart, enough connective tissue forms to stop excessive bleeding. When necessary, transfusions and other supportive measures are given before cancer treatment is started.

Complications appearing during subsequent visits of the patient are usually due to spread of the malignant lesion, uncontrolled by the previous radium therapy. Limited radium therapy usually affords some palliation in the presence of late complications.

As to future developments in the treatment of cervical carcinoma, everything possible for early detection of the growth should be attempted. Diagnosis by the vaginal smear and cancer prevention clinics should prove of value. In early carcinomas, Wertheim hysterectomy plus irradiation, or radium therapy alone, offers a good prognosis. Another hopeful development for a limited number of patients is Taussig's iliac lymphadenectomy, combined with radium therapy to the primary growth.

Cancer of the uterine fundus is not as insidious as carcinoma of the cervix, the lesion is of lower grade microscopically and grows more slowly, affording time for recognition and proper therapy. At the Clinic, an attempt has been made to divide the lesion into 4 stages. In stage 1 the lesion is limited to the uterine cavity within the level of the internal os and the uterus is movable and not enlarged. In stage 2 the uterus is movable but definitely enlarged, the growth infiltrating the fundal walls. In stage 3 definite infiltration of the parametrium on one or both sides with limited mobility of the uterus has occurred, or infiltration on one side with fixation of the uterus, or infiltration of a large part of the cervix, or in some cases isolated metastatic growths to pelvic lymph nodes with a small primary growth. In stage 4 the uterus is enlarged and fixed with remote

revival of radical operation which has been advocated for a selected group of patients. Similar standards of proficiency and experience of course should apply to the much more frequently indicated radiotherapeutic plans.—Ed.)

RADIUM THERAPY OF CANCER OF THE UTERINE CERVIX AND OF THE FUNDUS

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The prognosis of cancer of the cervix depends on the stage or anatomic extent of the lesion and on the grade or microscopic appearance. About 90 per cent of cervical cancers are squamous cell epitheliomas and of these about 85 per cent are grade 3 or 4 (Broders' method), a rapidly growing type of cancer. At the Clinic, 90 per cent of the patients are in stage 3 or 4 (League of Nations definition) when referred for radium therapy.

In the treatment of cervical cancer, the author stresses the importance of early diagnosis and of cooperation of the clinician, pathologist, radiologist and surgeon. The plan of radium therapy at the Clinic is defined as an intensive broken dose method. A 50-mg. platinum-filtered tube is the unit of treatment and the average advanced lesion receives a total dose of 7,000 to 8,000 milligram hours throughout the entire birth canal in approximately 8 applications in a period of 3 weeks. At the beginning, treatments are applied twice a week and more rapidly thereafter, the exact interval depending on the visible response of the tumor. The main principles of treatment are: (1) homogenous irradiation of the entire birth canal, by fairly short repeated treatments; (2) avoidance of trauma in probing the canal and in inserting the tube; (3) use of the knee-chest position for adequate exposure and to avoid trauma during the necessary manipulations; (4) use of adequate gauze packing above the tube to increase the distance of the intestinal wall from the element; and (5) adequate follow-up studies of each patient over many years.

Following the radium treatments, a supplementary course of roentgen therapy is given, at 200 kv., using 550 r measured in air to each of 4 fields, in hope of sterilizing the parametrial regions. In stage 3 or 4 lesions, this course of roentgen therapy is repeated 3 months later. Thus, irradiation therapy at the Clinic is primarily radium treatment, with supplementary help from roentgen therapy. The writer feels that in carcinoma of the cervix, as in cancer in other accessible locations, radium is a superior agent if properly employed, with roentgen therapy as a valuable adjuvant.

A review of several hundred cases in which radium treatment was used at the Clinic, published a few years ago, showed patients with stage 1 lesions to have a

tensive, of squamous epithelium, but the essential and the malignant portions of such tumors are the adenocarcinoma. The squamous portions are an adventitious factor, and they are not in themselves malignant. Similar patches are at times found in obviously benign hyperplasia of the endometrium. The mistake should not be made, as is done by some, of considering such squamous areas in adenocarcinoma as indicative of combined adenocarcinoma and squamous cell carcinoma.

The generalization expressed by the author in the last paragraph will be endorsed in essence by most gynecologists, i.e., that carcinoma of the cervix is primarily a radiologic problem, with some exceptions and qualifications; and that carcinoma of the corpus is primarily a surgical problem, with again some exceptions and some qualifications, such as the usual advisability of preliminary radiation.—Ed.)

TREATMENT OF CARCINOMA OF THE UTERINE CERVIX; CONSIDERATIONS ON THE FIFTIETH ANNIVERSARY OF THE WERTHEIM OPERATION

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During the past 50 years the treatment of carcinoma of the cervix (up to then incurable) has pased through 2 distinct phases, the surgical and the radiological approach. The development of the radical hysterectomy as recommended in 1895 by Ries and elaborated upon by others, including Wertheim, brought a ray of hope for then hopeless sufferers. The fundamental change toward irradiation therapy came when at the meeting of the Academie de Medecine de Paris in April, 1932, Jean Louis Faure presented his results with radical surgery and was challenged at another meeting in May, 1932, by the presentation of Regaud's results obtained by radiation therapy in the Institut Curie. Comparing comparable stages of the disease, Regaud has shown that his radiological results were superior to the surgery of Jean Louis Faure, and that still considerable salvage could be obtained in inoperable cases, and that at the same time the primary mortality for radiation therapy was incomparably lower than for surgery. All over the world, in leading institutions, radiation therapy was accepted as the method of choice for treatment of epidermoid carcinoma of the uterine cervix.

The radiation therapy which the authors have used during the last 10 years, and on which this discussion is based, essentially follows procedures developed in the Institut Curie by Regaud, Lacassagne and Coutard. To appraise the exact extent of the disease, they follow the classification proposed by the League of Nations (1937).

In addition to the examination of the patient necessary for classification (palpation, inspection and cystoscopy), the authors use routinely, in every case beyond Stage I, an intravenous pyelogram in order to determine a possible obstruc-

metastatic growths in many cases of general carcinomatosis. Endometrial biopsy in most of the Clinic's cases showed at least 75 per cent of the lesions to be adenocarcinoma, around 11 per cent squamous cell epithelioma and the remainder not diagnosed as to type of cell. Grades 1 and 2 were present in at least 56 per cent of cases, grades 3 and 4 in only about 31 per cent.

In the treatment of cancer of the uterine fundus, complete hysterectomy usually achieves a cure. Radiologists are interested in 2 groups of cases: those in which the lesion has extended widely before the diagnosis was established, so that surgical treatment is no longer feasible, and those in which the lesion is still small but the patients are poor operative risks. In earlier years radiologists were not anxious to treat these lesions; however, better results than expected with irradiation of carcinoma of the rectum and of obviously inoperable carcinoma of the uterine fundus gave more encouragement for irradiation of cancer of the uterine body. A review of results in patients treated with radium at the Clinic from 1925 to 1935 showed 39 per cent 5-year survivals. In 40 per cent of the 109 cases the lesions were of stage 1 or 2, compared with only 21.5 per cent in an earlier series, in which only a 12.63 per cent 5-year survival rate had been obtained.

The underlying principle of treating cancer of the corpus is homogenous irradiation of the entire birth canal, employing the intensive broken dose method. Following diagnostic curettage, two 50 millicurie radon tubes in tandem formation filtered with 0.5 mm. of silver and enclosed in a 1 mm. brass tube are introduced to the depth of the uterine canal for 24 hours. About a week later a second tandem is used, this time in the midportion of the uterus. The interior of the uterine corpus receives from 4,800 to 7,200 millicurie hours in a period of 3 weeks, more than one intra-uterine treatment a week never being applied. Cervical and vaginal treatments may be given in the interval. The radium treatment is followed by a course of high voltage roentgen therapy, 550 r per field for 4 to 6 fields around the pelvis; this may be repeated 3 months later in more extensive cases.

Thus, carcinoma of the cervix is primarily a radiologic problem, except in the few cases in which early diagnosis is made. On the other hand, carcinoma of the corpus is primarily a surgical condition for the patient in good general health; however, irradiation can accomplish a great deal for patients who are poor surgical risks. 5 figures.

(The 69.2 per cent 5-year survival rates in Stage 1 cases and 60.2 per cent in those of Stage 2 represent excellent results, which, incidentally appear definitely better than those reported from the same clinic by Masson in the preceding abstract, if one is justified in the assumption that the latter's series included only those which are ordinarily considered to justify operation, those of Stage 1 and at least some of Stage 2.

The classification of corporeal carcinoma described by the author is much like that employed by others. However, it is surprising to read that 11 per cent of the corpus cases showed squamous cell epithelioma, which in most clinics has been found to be so rare in the corpus as to be almost disregarded. One can only wonder whether cases have been included in which cervical epidermoid carcinomas have extended upward into the cervix, or, as is more likely, whether there has not been an inclusion among the squamous carcinomas of the so-called adenoacanthomas. In the latter one finds plaques, sometimes numerous and ex-

tissues. During the course of radiation therapy, the patient's general routine has to be adjusted to the treatment. Unnecessary fatigue and nervous excitement should be avoided and the diet should be adjusted to the anticipated intestinal reactions. The main by-effects of radiation therapy which cannot be completely avoided even under ideal circumstances but which can be minimized by careful attention to details, are the radiation damage to the rectal mucosa, bladder mucosa, and a fibrosis of the pelvic vasculo-connective tissue.

The results of treatment of 310 cases are presented, showing a 5-year-cure rate of 83 per cent for Stage I, 56 per cent for Stage II, and 38 per cent for Stage III.

A critical evaluation of the results of radiation therapy in comparison with radical surgery still leads to the convincing conclusion that adequate radiation therapy yields, even in operable cases, results at least equal to excellent surgery, if the problem is viewed from a statistical point of view. Radiation therapy of carcinoma of the cervix, as radiation of other cancers, should not follow any preconceived outline or rigid technic. The anatomy, the disease and the constitutional reaction of the patient to this disease and to the treatment are the guiding factors at all times. Radiation therapy of cervical cancer has superseded surgery and is accepted as the superior procedure of choice because in the overwhelming majority of cases it accomplishes more with less risk, if properly used. The sound of voices advocating a return to surgery should rather stimulate us to improve radiation therapy to greater accomplishment.

(The plan of treatment outlined by the authors has apparently justified itself by the remarkable results obtained. It of course differs in technique and dosage from methods employed by many others, for there is the widest variability in this respect. One comment made by the authors which merits underscoring is that no preconceived plan is applicable to all cases, but that there must be much flexibility and individualization. If results similar to those reported by the authors, 83 per cent of 5-year cures for Stage 1 and 56 per cent for Stage 2, could be achieved in all clinics, then indeed one would expect a stilling of "the voices advocating a return to surgery."—Ed.)

THE EARLY DIAGNOSIS OF CANCER

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In May, 1937, as a cautious experiment a special clinic day was designated in the Kate Depew Strang Tumor Diagnostic Clinic of the New York Infirmary for the complete physical examination of apparently healthy women who were anxious to know if they had cancer. This was the first organized attempt toward possible prevention and early diagnosis of cancer. It was a tentative

tion of the ureters. They feel that the demonstration of a ureteral obstruction places a case that otherwise might be staged as III or II, in Stage IV since it makes the prognosis almost hopeless. This staging is entirely based on clinical findings and does not permit us to know the true pathological extent of the carcinomatous involvement. Two fallacies must be kept in mind: the interpretation of an inflammatory palpable parametrial infiltration as carcinomatous, and the actual presence of clinically demonstrable carcinomatous lymph nodes in higher portions of the pelvis beyond reach of the palpating finger.

The miscroscopic grading of epidermoid carcinoma of the cervix has been found of only very limited importance in treatment and prognosis, with the exception only of the extremely anaplastic carcinomas, which show a high degree of spontaneous necrosis and infection.

In evaluating the probable result of radiation therapy, care should be taken to eliminate the small number of adenocarcinomas of the cervix originating from the cervical glands, and of those cases of adeno-acanthomas of the cervix which have developed on the basis of adenocarcinomas of the cervix with secondary metaplasia into squamous cell carcinoma. These types do not respond as favorably to radiation therapy.

Complete radiation therapy for carcinoma of the cervix in all cases but Stage I consists of a combination of local radium application and external roentgen therapy. The radium application is directed toward the primary focus of the disease in the cervix, the roentgen therapy toward the parametrial infiltration. Following the experience of Regaud and Lacassagne, the writers attempt in each case to give a total dose of 8000 mg. hours, equally divided into 4000 mg. hours through a cervical tandem and 4000 mg. hours given through paracervical applicators. Minute attention is given to details of the anatomical distribution of the radium as well as to the anatomy of the individual patient. In the majority of cases the cervical as well as the vaginal applicator is inserted under anesthesia. This causes a relaxation of the vagina and improves the possibility of inserting enough packing between the applicators and the vaginal walls to establish a maximum distance between the radium and the rectal and vesical mucosa.

The authors emphasize the extreme importance of the proper distribution of the radium dose in time. They are convinced that many of the failures reported in the literature, with regard to incomplete sterilization of the focus in the cervix itself as well as to severe rectal and vesical complications, are due to too rapid and too concentrated treatment.

In all stages but Stage I, this application of radium is followed by a course of external roentgen therapy. On the average, a total dose to all fields of approximately 12,000 r, measured on the skin, is given in a period of about 6 weeks. A total dose of 14,000 r on the skin has not been exceeded.

In general, the writers attempt to start the treatment with radium therapy which is followed by x-ray. Since the radium treatment constitutes the most important part of the procedure, they do not wish to jeopardize the possibility of carrying the radium dose to the upper limit by complications which may ensue from external roentgen therapy carried to the limits of tolerance of the normal

deserve a prominent place in all gynecological examinations. They are of especial significance for the reason that they may indicate the presence of early carcinoma before other gross signs or clinical symptoms are present. The positive diagnosis of cancer, however, must rest on the histological report of a surgical biopsy or a uterine curettage.

A rather interesting experience with the Papanicolaou smears is described. A young woman with vaginal bleeding from whom 2 positive smears were obtained was recommended to have a uterine curettage. However, the curettings were negative for cancer. Since the symptoms continued, a laparotomy was performed on the probable diagnosis of ovarian cyst, and a bilateral carcinoma of the fallopian tube was found.

What has been learned in the past 9 years from this cautious experiment in early diagnosis and possible prevention of cancer? In 1945, 3066 new patients were examined and 3161 return visits were made, giving a total of 6227 patients in one year. About 40 per cent of all these persons came to the clinics without symptoms or noticeable evidence of disease. Of these, 1.5 to 2 per cent, varying from year to year, were found to have early cancer. About 20 per cent had benign tumors, and 9 per cent had precancerous lesions. Only 16 per cent had no evidence of disease. The rapid growth of the clinics demonstrates the willingness and desire of the people to accept such a program.

(The Tumor Diagnostic Clinic conducted by the author is a pioneer in the cancer detection movement which in more recent years, through the motivation and financial support of the American Cancer Society, has attained such widespread proportions. The results reported by the author leave little doubt of the value of such clinics, not only in the not infrequent unearthing of unsuspected early cancer, but probably even more as centers of cancer education for increasingly large numbers of women, all of whom are in turn likely to spread the saving gospel among other women.

The author takes a very sane stand as to the relative value of biopsy and vaginal smear studies, the former being the method of choice, as it should be, in the presence of a suspicious lesion. On the other hand, it seems to me that the ideal application of the vaginal smear method is in cancer detection clinics, where such an overwhelming proportion of the patients have no clinical suggestion of cancer. The screening of such presumably normal women by smears is quite sure to yield an occasional positive case in which the indication thus becomes clear for intensive study. The incidence of such accidental finds thus far has been small, but they are well worth the effort. It is unfortunate that in the now numerous cancer detection clinics, in which vaginal cytology studies would seem to have their ideal application, only a small proportion have made use of the procedure. However, I understand that plans are on foot on the part of the American Cancer Society and the U. S. Public Health Service, to make this procedure feasible in many more clinics.

Some time ago, in an editorial comment on primary carcinoma of the tubes, a disease rarely diagnosed preoperatively, I mentioned the fact that positive vaginal smears, in the absence of any demonstrable pathological lesion of either the cervix or corpus, might be of possible value in the diagnosis of tubal or perhaps even ovarian carcinoma, but that no case, so far as I knew, had been reported in which this method had been applied in the diagnosis of tubal carcinoma. The case of unsuspected tubal carcinoma reported by L'Esperance, however, confirms the validity of the method in the diagnosis of tubal carcinoma, although in this case the existence of the tubal neoplasm was altogether unsuspected, as it almost always is because of its very great rarity.—Ed.)

plan to prove whether prevention and early diagnosis in cancer could become a practical part of a medical health service.

These clinics rely almost exclusively on the periodic manual examination of the breasts in all cases as the most satisfactory guide for further diagnostic investigation of any disease in the breast. In the presence of suspicious lesions, all special aids in diagnosis of breast cancer are brought into action, including transillumination of the breast, soft tissue x-ray, and the aspiration biopsy.

The most frequent cancer in women is that involving the uterus and it is responsible for about 30 to 35 per cent of deaths from this disease. In the recognition of early cervical carcinoma, every diagnostic aid is employed. The Papanicolaou vaginal smears and the direct cervical smear occupy an important place and are routine in all cases. In the presence of a suspicious lesion a surgical biopsy is the method of choice. The role of surgical biopsies in the early diagnosis of cervical cancer can hardly be overemphasized. During the past year at Memorial Hospital, Stewart and Foote have confirmed 9 cases of intraepithelial epidermoid carcinoma—carcinoma in situ—by this means, when simple surgical amputation may be effective. Pund and Auerbach who examined, in serial sections, 1200 surgically removed cervices, state that preinvasive carcinoma was discovered in 3.9 per cent. The average age of the patients was 36.6 years as contrasted with 48 years, the usual age of fully developed cancer of the cervix. This seems to substantiate the theory held by Ewing and Stewart that the latent period of quiescent cancer may be from 5 to 10 years or more, and that the carcinomatous process is a distinctly evolutionary one having a local starting point and pursuing a known course to a definite termination.

Prevention and early diagnosis of carcinoma of the fundus are more difficult and dependence should be placed on the routine vaginal examination as the most effective measure associated with the endometrial aspiration biopsy. Smears by the Papanicolaou method are useful in determining the necessary future steps to determine a diagnosis. In the author's experience, if repeated positive smears are obtained and no evidence of cervical disease is observed, it is an indication for uterine curettage to determine the presence or absence of fundal carcinoma. The significance of these positive smears is not always evident to the general practitioner, as is illustrated by the case of a patient with 3 positive vaginal smears who was referred to her physician with the report of these findings and information that this indicated the necessity of uterine curettage. Three months later the patient reported that her physician had not deemed the operation necessary. The smears were again positive and her physician was so notified. Six months later she returned with uterine bleeding and a fully developed adenocarcinoma of the fundus.

The most important single method at the disposal of these clinics for the early diagnosis of cancer is the comprehensive periodic physical examination of an individual by a physician alert enough to recognize early signs of cancer. This examination is not limited to any part of the body.

The writer states that vaginal smears by the direct or Papanicolaou method

The authors were able to check only 35 cases with tissue obtained at surgical dilatation and curettage or hysterectomy, excluding cases preoperatively radiated. This is explained by the fact that they often did not burden their pathologist with study of surgical curettings at the time radium was applied to patients whose previous biopsies showed cancer, and that practically all corpus carcinoma received preoperative radiation. Of the 35 cases checked, it may be noted that "surgical" diagnosis agreed in full with "aspiration" diagnosis in 26 cases and partly agreed in 2 cases, a total of 80 per cent agreement. Surgical diagnosis disagreed positively with aspiration only twice: (1) a patient whose aspiration curettings were reported insufficient was found to have carcinoma of the endometrium at curettage 10 days later; (2) another aspirated insufficient was found to have hyperplasia at curettage 14 days later.

Carcinoma of the endometrium plus malignancies of the upper cervix and ovary accounted for 33.4 per cent of the postmenopausal patients' symptoms of abnormal bleeding or discharge without obvious cause, as contrasted with only 3.5 per cent in the premenopausal group.

(While endometrial aspiration biopsy is a very valuable procedure, and while I employ it extensively in the study of functional problems, especially female sterility, I would hesitate to depend upon it for the diagnosis of so grave a disease as cancer. The procedure is, in my opinion, the simplest and most practical method of determining the occurrence or non-occurrence of ovulation, in spite of the fact that it may in the occasional case be misleading, though evidence on the latter point is as yet extremely scant.

But when one is on the search for early adenocarcinoma curettage should be extremely thorough, and my own practice is to employ for this a light pentothal anesthesia. This need not involve hospitalization, as most patients can leave the hospital in an automobile within an hour or so, with directions to rest for a day or two at home. Aspiration curettage without anesthesia cannot be quite as thorough in all cases. Some patients have very little discomfort, but others, especially those of apprehensive type, experience considerable pain for the very short time necessary for the procedure, and the surgeon is apt to feel hurried and to do a less meticulous curettage than if the patient were anesthetized.

The chief role of the somewhat over-publicized vaginal smear method of diagnosis would seem to be in cancer detection clinics, as a screening method in presumably normal women. I do not know just how its results would compare with aspiration curettage, although I suspect that the latter, even with its shortcomings, would be of greater general value. What I have said above as to the importance of thorough curettage under anesthesia applies especially to cases in which because of bleeding there is at least some clinical suspicion of cancer, but there would of course be no justification for this plan as a part of cancer detection clinic routine.—Ed.)

EXPLORATORY EXCISION AND COLPOSCOPY IN EARLY DIAGNOSIS OF CARCINOMA OF THE PORTIO

G. Mestwerdt

Jena, Germany

More than 60 years have passed since Ruge and Veit first proclaimed the necessity for microscopic examination of tissue in the diagnosis of uterine carcinoma,

ASPIRATION CURETTAGE OF THE ENDOMETRIUM IN A CANCER CLINIC; AN ANALYSIS OF 200 CASES

G. A. WILLIAMS AND C. B. STEWART

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As a result of this study, the authors wish to emphasize that aspiration curettement is a useful procedure in the study of the endometrium if properly applied and properly interpreted. Its chief advantages are immediate acceptance by the patient, and economy, in that neither hospitalization nor anesthesia is required. However, it should not be presumed that they recommend this method to displace more generally accepted measures. Neither are they in a position to compare it with the efficiency of vaginal smears as a screen in such patients.

In 1939 the number of patients with unexplained abnormal bleeding and/or discharge in the authors' clinic became so large that it was impossible to hospitalize them. Aspiration curettement was instituted as a screen measure. The cannula used consisted merely of a size 12 metal male catheter with a knife edged fenestrum on the convex side of its shortened beak. After sounding carefully for direction of the canal, dimensions of the cavity and irregularities of its surfaces, the cannula is introduced and the fenestrum applied firmly to one border. Suction is then applied while the fenestrum is moved over the entire endometrial surface. The contents of the cannula are ejected into normal saline solution and the fragments of endometrium are carefully separated out, to be placed in formalin or Zenker's solution.

The 200 cases analyzed in this paper were consecutive and unselected from patients 36 years of age or older, except that neither those diagnosed previous to referral to the clinic nor those aspirated by interns in the first 6 months of service are included. Only cases followed up adequately for a period of 2 to 6 years were included.

The initial pathologic diagnoses in the aspiration curettings were as follows:

Insufficient tissue	12.0%
Proliferative	12.0%
Proliferative and secretory	0.5%
Secretory	11.0%
Hyperplastic	34.5%
Atrophic	6.5%
Chronic endometritis	11.5%
Cervical polyp, precancerous	1.0%
Adenocarcinoma of endometrium	9.0%
Adenoacanthoma of endometrium	0.5%
Epidermoid carcinoma of cervix	1.0%
Adenocarcinoma of cervix	0.5%

The final diagnoses in the 24 cases of insufficient tissue included 2 cases of carcinoma of the cervix and one case of carcinoma of the endometrium.

and its technique is difficult to master. It would be well, however, for the general practitioner who is active in gynecology and whose chief task is early diagnosis to become familiar with its use. For the specialist such training is indispensable, as colposcopy, in conjunction with all other known resources in the fight against cancer, marks a forward step towards early diagnosis, and consequently a higher percentage of cures.

(This paper is a plea for the wider use of the colposcope as an aid to the early diagnosis of cervical cancer. Following the introduction of colposcopy by Hinselmann, the method quickly became popular in many of the continental clinics, and was taken up by a few in this country. It has long since been virtually abandoned here, the general feeling being that not much additional information is gained by examining the cervix under colposcopic magnification over that yielded by meticulous inspection of the cervix in the best possible light. Moreover, the procedure is a laborious and time-consuming one, as all those who have employed it can testify, and it takes much experience to interpret the visual findings. For this reason I do not agree with Mestwerdt that general practitioners should be encouraged to use the colposcope.

It is of interest to note that the method is still quite widely used, especially in Germany and in Switzerland. The excellent recently published book by Hansjakob Wespi, of Basel (Benno Schwabe & Co., Basel, 1946), entitled "Entstehung und Frühererfassung des Portiokarzinoms," is based almost entirely upon the systematic employment of colposcopy. It contains many excellent photomicrographs of preinvasive and early invasive carcinomatous lesions, and the author is obviously an enthusiast for the method.

Now that we are all becoming so interested in early preclinical and preinvasive lesions, I have been wondering whether it might not be worthwhile to go back and take another fling at colposcopy, although even now it seems difficult to believe that it would be of more than slight supplementary value to other more decisive methods, especially the examination of comprehensive surface scrapings in cases with no visible lesion to indicate a fruitful site for the ordinary biopsy.—Ed.)

RESULTS FROM TREATMENT IN ADENOCARCINOMA OF THE CERVIX

BRIGIT SCHINK

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The question as to whether a glandular carcinoma of the cervix uteri can be cured by x-ray treatment alone, or whether a radical operation is preferable, is still a debatable one according to many authorities. The author of this paper presents a study of the results obtained by x-ray treatment in a number of cases, in an effort to shed further light on the subject. She prefaces her survey with a discussion of the difficulties presented in the treatment of carcinomas of glandular type. Such carcinomas spread into the muscular walls and the perivascular lymphatic ducts leaving considerable healthy tissue in between. They

and inaugurated the practice of exploratory excision of tissue for this purpose. Today it is the standard method, and its findings determine the nature of the therapeutic procedure.

Clinicians and histo-pathologists agree that the accuracy of the histological diagnosis depends on the proper excision of tissue from the right spot and the dimensions of the specimen thus obtained. While existing records show that 85 per cent of biopsies are unnecessary, many carcinomas might be overlooked without their use, but greater accuracy and better results might be attained through broadening the present diagnostic procedure.

This has been made possible through use of the colposcope instead of the ordinary vaginal speculum. Existing records show that colposcopic examinations between 1943 and 1945 reduced to 1/10 the number of biopsies made in an equal number of cases between 1933 and 1935. These figures taken from the charts of patients in the Women's Clinic at the University of Jena show that the preliminary use of the colposcope also reveals atypical epithelial changes indicating the advisability of biopsy. Thus, between 1943 and 1945, in 66 cases 22 carcinomas were discovered in excised tissue where the colposcope showed an atypical epithelium.

These histological examinations were made from material obtained from the region of the os uteri, and in 60 of these cases more extensive exploratory excisions were carried out in the form of serial section examinations.

For the elucidation of these figures it should be explained that there are many difficulties, at least in the first stages of carcinoma, in determining whether histologically revealed epithelial changes should be classified at once as carcinomatous, and opinions differ on this point. When do the histological findings leave no doubt as to the existence of a carcinoma? It is unanimously agreed that the structure of the epithelium must show marked changes, such as alterations in all its layers, a multiple change of form and increase in numbers of the nuclei, an augmentation of their segmentation, their capability for being stained and their arrangement.

Borst, whose authority is undisputed in the diagnosis of carcinoma advances the view that the development of carcinoma is always preceded by atypical alterations in the epithelium. Carcinomas discovered by biopsy reveal a destructive penetration of the epithelium into the connective tissue and a blockage of the surface excretory ducts. In addition, invasion of the glandular ducts and the lymphatic fissures, followed by a penetration of the basement membrane and the capillary system may be observed.

Figures from other sources show that many microcarcinomas have been identified in surface epithelium showing more or less notable changes. The results of 143 simple biopsies after ordinary speculum examination were 18 diagnoses of carcinoma, as compared with 80 biopsies in conjunction with the colposcopic examination, resulting in the discovery of 25 carcinomas. The records cover the years 1933–1935 and 1943–1945 respectively.

The use of the colposcope as a means for the early diagnosis of carcinoma through the detection of epithelial changes is by no means general as yet,

Finally, the author proceeds to emphasize the necessity for a periodical examination of all patients discharged from the clinic as cured. She cites one case in particular in which recurrence was suspected and followed promptly by roentgen ray treatment. Six years later the patient was well, although upon the first examination there was an infiltration of both parametria. Recurrence was detected in 11 patients at intervals of from 4 months to 5 years. She concludes her survey by stating emphatically that recurrent adenocarcinomas of the cervix are refractory to x-ray treatment unless detected in the early stages—hence the principal problems in connection with their treatment are the discovery of methods making early diagnosis universally possible, and the detection of recurrence at an early stage.

(Most gynecologists would probably agree that cervical adenocarcinoma responds less favorably than the epidermoid variety to the radiotherapy usually employed, and that while this is by far the least common variety of uterine cancer, it is probably the most malignant. Aside from its frequent unresponsiveness to radium, the common location of the lesion within the cervical canal makes it more insidious, since bleeding, especially of the contact variety, is apt to occur later than in the more external epidermoid variety. When the lesion is discovered in an operable stage, and especially if it fails to respond to radiotherapy, radical operation would seem to be a wise plan.

The importance of careful follow-up of all cervical cancers is obvious, for, as Schink emphasizes, even when a recurrence occurs, further radiotherapy may check its extension, even for many years. All sorts of vagaries may be noticed in this respect. I recall a patient with recurrence of an epidermoid carcinoma in the vaginal vault 2 years after operation. This, after biopsy, was destroyed locally with the cautery and the patient then given further irradiation. She was still living and apparently free of further recurrence 4 years after the above.—Ed.)

SARCOMA OF THE CERVIX UTERI

R. F. Matters

M. J. Australia, 1: 796, 1947

The case was discussed of a married female who was admitted to the hospital originally with a diagnosis of cervical polypus and fibromyomata uteri. Biopsy of the polypus revealed sarcoma, but for unknown reasons the patient was discharged without further measures being taken. Later, a private medical practitioner performed a subtotal hysterectomy. Hemorrhage and dysuria continued until the patient was first seen by the author.

Examination revealed a mass the size of a fetal head filling the vagina. Examination of sections of the mass showed spindle cell sarcoma. The mass was removed by diathermic *morcellement*. Dr. Matters said that relief of bowel and bladder symptoms was remarkable, but the outlook was hopeless. Had panhysterectomy been performed in the first instance, the prognosis might have been good. At the time this report was presented, metastases had occurred which were beyond any but palliative measures.

progress with extreme rapidity and an examination often reveals conditions which preclude the use of the knife or the x-ray, as too much sound tissue must be sacrificed for the complete extirpation of the carcinoma.

Poor sensitivity of glandular cells to x-ray has been observed by many authors, among them Kehrer, Lahm and Adler, who consider adenocarcinoma as almost completely refractory to irradiation, and therefore favor operation. Lacassagne is more cautious, believing that adenocarcinoma is not entirely insensitive to x-ray treatment, but considers it perhaps wiser to operate. Phillipp and Markulicz reach the same conclusion. Doederlein observed a number of cases in which the primary reaction to irradiation was favorable. Von Franque, Haupt and Madruzza give the method qualified approval. On the other hand, Wintz, a staunch supporter of x-ray treatment alone in cases of adenocarcinoma, published statistics showing 47 per cent of permanent cures in cases treated by this method. A later compilation by Ruckert covering the period between 1920-1941, showed 28.6 per cent of cures through operations at the Koenigsberg Women's Clinic, as contrasted with 12.03 per cent in cases given treatment with x-ray.

The author describes 34 cases diagnosed as adenocarcinomas at the Women's Clinic at the University of Jena between 1927 and 1941. A thorough study of the material was hampered by war and post-war conditions, as complete data were lacking owing to the destruction of files in the registrar's office through bombings and conflagrations. Three patients were never heard of again. Those still living were examined periodically after treatment, and where transportation facilities were lacking, questionnaires were sent out.

The treatment in the overwhelming majority of cases consisted of irradiation by radium and roentgen rays. Only 3 of the 34 patients were operated upon. In conjunction with these operations an immediate small intravaginal dose of radium was administered (400–500 mg. El. St.) and repeatedly renewed. This treatment was followed by 2 series of roentgen ray treatments, one 2 to 4 weeks later, the other in from 3 to 6 months.

The radiotherapy was applied in the same doses as those used in cases of carcinoma of squamous cell type, and in the following manner. First, curettage or removal of slough from the tumor with the electric incandescent sling; next the first radium irradiation in the corpus uteri. The average dosage was 5000–6000 mg. El. St., administered in 2 treatments. In 1940, mesothorium came into use. The dosage was increased or diminished according to individual requirements. Later a radium unit was obtained which was administered in 3 doses of 2000 mg. El. St. each.

The first roentgen ray treatment was usually administered 8 days after the first application of radium, the second 3 months later, followed by further treatments when indicated. Between 1929 and 1938 the roentgen ray treatment was frequently supplemented by treatment with Splendothelan and the Fischers-Keysser serum.

Of the 34 cases listed 7 were alive with no recurrence of the carcinoma after 5 years. A relative cure was shown in 30.7 per cent of the operable cases and in 14.3 per cent of the inoperable cases.

ing. Especially in women of the immediately pcstmcnopausal group, one should never fail to make sure that the patient has not been getting oral or hypodermic estrogen therapy. As is evident from the paper, many other causes than carcinoma may be responsible for postmenopausal bleeding. Some give the proportion of cancer etiology as something over 50 per cent, some as considerably less than 50 per cent. In any event, the proper sort of investigation, often an interesting diagnostic problem, will usually resolve the matter, and point the way to either very simple conservative or definitely radical therapeutic procedures.—Ed.)

A FATAL CASE OF PRIMARY DIPHTHERIA OF THE CERVIX AND URETHRA

JANET BOTTOMLEY AND D. R. CHRISTIE

J. Obst. & Gynaec. Brit. Emp., 54: 375–376, 1947

The case is presented of an unmarried woman who was admitted to a British military hospital in Germany in May, 1946, having started an illness of influenza type 2 days previously. Examination revealed tenderness in both iliac fossae, and a diagnosis of salpingitis was made. When seen by the senior author the patient complained of breathlessness and chest pain. Throat, heart and lungs appeared normal. The urethral meatus was inflamed and there was a thin discharge. The cervix was red, with some discharge. Cultures from both the urethra and cervix showed *C. diphtheriae*, identified as *mitis* strain. Nose and throat showed no *C. diphtheriae*.

Treatment was given with intramuscular anti-diphtheritic serum 96,000 units, and an intramuscular drip of penicillin. Polyneuritis and myocarditis were already present when treatment was started. The urethral inflammation cleared up. After treatment, clearance swabs from the cervix were negative, but the patient's general condition deteriorated. The myocarditis progressed, the patient had a vagal block attack and died after further collapse which failed to respond to restorative measures.

When diphtheria was diagnosed the patient was questioned as to possible contacts, and she stated that her "betrothed" had shared a prison cell 6 weeks previously with a man who had diphtheria. Swabs were later taken from the betrothed; *C. diphtheriae mitis* was found in the throat swab, but not in urethral swabs.

Although opinion is divided on the severity of this condition, the authors state that there are sufficient numbers of toxic and fatal cases on record to indicate that the matter is a serious one.

(While primary diphtheria of the cervix or urethra, or both, is extremely rare, a number of cases, some fatal, have been observed. In most of them there has been no explanation of how the organisms find their way into the vaginal canal, and the authors of the present paper do not speculate on this point in the description of their case.—Ed.)

(Cervical polyps are characteristically of rather soft and fragile texture. When a polyp has a very solid and brawny consistency, one must suspect the possibility of sarcoma. It should be remembered that a small proportion of uterine sarcomas are of endometrial or endocervical origin, and that both these varieties have a tendency to the formation of polyp-oid outgrowths from the surface, usually of very heavy and bulky structure. I recall at least 2 cases in which the microscopic examination of excised cervical polyps led to the diagnosis of previously unsuspected sarcoma of the uterus.—Ed.)

POST-MENOPAUSAL UTERINE BLEEDING

J. W. Harris

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Marquette M. Rev., **12:** 207–209, 1947

In determining the etiology of post-menopausal bleeding, the physician must first limit or localize the bleeding to the generative tract itself. Rare though they are, certain general systemic conditions may cause bleeding. In all cases there must be careful inspection and palpation of the generative tract, particularly of the cervix.

The cervix is perhaps the commonest single cause of bleeding in the post-meno-pausal woman. Cervicitis and cervical erosions may cause a bloody vaginal discharge. A common source of cervical bleeding in this age group is cervical polyps. It is well to remember that a considerable percentage of both cervical and endometrial polyps show definite malignant changes, and any polyps removed from either area should be carefully examined microscopically. Another cause of post-menopausal bleeding is prolapse of the cervix in association with polyps.

Uterine endometrial polyps occur more frequently and are more prone to be malignant than cervical polyps. All in all, the commonest single cause of uterine bleeding in the post-menopausal woman is carcinoma of the fundus.

One should not forget that large doses of synthetic estrogens, and sometimes small doses, literally produce bleeding. Cases have been recorded in which post-menopausal bleeding was directly due to the use of beauty creams containing es-trogens. Also, one should bear in mind the carcinogenic effect of estrogens when given over a long period of time.

The most valuable diagnostic aid is careful examination of the cervix—what it looks like. Another valuable procedure is the biopsy; it is better and safer to hospitalize the patient and thoroughly scrape out the uterus under anesthesia than to perform an office biopsy.

(This is a very sound and authoritative short review of the subject. The author wisely calls attention to the still widespread abuse of estrogens, especially those of the nonhor-monal group represented most frequently by stilbestrol, as causes of postmenopausal bleed-

(The lowly vaginal pessary has become a neglected instrument in the practice of many gynecologists, and there are many medical schools in which students receive little or no instruction as to its mechanism, its indications or its contraindications. As the author states, it is often of value to the obstetrician in the management of the prolapsed or retro-flexed uterus of early pregnancy, just as it is in that of puerperal retrodisplacements, often usefully combined with knee-chest postural treatment.

The gynecologist also finds not infrequent indications for the use of the pessary. In addition to those mentioned in the abstract, the proper use of the pessary will often keep quite comfortable the aged woman with a prolapse, who might prefer this to even simple operations of the Lefort type, or in whom any sort of operative treatment is not desirable because of serious systemic disease.

When it comes to cervical stem pessaries, not many nowadays would endorse their employment for primary dysmenorrhea, a formerly favorite treatment, still used in a few clinics. Troublesome cervicitis, not to speak of the occasional more serious pelvic infection, is the chief hazard, while the very rationale of the plan is open to serious question.

My experience is that hospital internes and residents are as a rule quite ignorant of the principles of vaginal pessary treatment, types of pessaries, methods of molding and fitting the pessary, and other such things, and some one should instruct them during their period of training. A cardinal rule is that the pessary is not meant to force the uterus into normal position, but simply to retain it once the uterus has been restored to approximately normal position by manual or postural means.

Every gynecologist of experience has seen instances of the harm which can result from too prolonged retention of a vaginal pessary, sometimes for many years, and usually due to the neglect of the patient. Sometimes, however, the doctor is at fault for not instructing the patient as to the importance of returning at regular intervals of 2 or 3 months to have the pessary removed, sterilized and reinserted. Pessaries neglected for many years may cut deep ulcerative grooves into the vaginal wall and bury themselves deeply in the latter, so that there may be much difficulty in removing them. This accident must have been a fairly common one in the old German clinics, and many years ago a German gynecologist (Pivnycka) devised a so-called pessariotome for the removal of such buried pessaries. Many years ago I saw the late Dr. Howard A. Kelly remove through the abdomen a pessary which many years previously had been inserted into the vagina.

Just a few weeks ago I saw an unusual instance of this general character. Among the vaginal types of pessary sometimes used by the older gynecologists was a solid or hollow glass ball. The patient was a woman of 65 who 16 years previously had had a hollow glass ball pessary of about the size of a tangerine introduced by a well-known gynecologist, now deceased. Recently she developed vaginal bleeding, and examination showed a marked annular senile constriction of the vagina, the canal being at this point of about the width of a lead pencil. The pessary could be seen and felt above this constriction. It was thought that the glass ball was probably hollow, as this form of pessary was more popular than the solid type. The removal of the pessary was possible only by a fairly extensive procedure, involving the employment of a Schuchardt type of incision.—Ed.)

MIGRATION OF OXYURIS VERMICULARIS TO LYMPH NODE OF ROUND LIGAMENT

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Although invasion of the upper portion of the female genital tract by *Oxyuris vermicularis* is not rare, so far as the author is aware, the finding of the adult

THE USE AND ABUSE OF PESSARIES

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West. J. Surg., 55: 544–549, 1947

This writer concludes that when rationally used, and when the precautions for their safe employment are taken, pessaries continue to be a valuable adjunct to the armamentarium.

Many agree that the retroposed gravid uterus is more liable to abort its contents than if it be replaced and held in correct anterior position by pessary. There is no argument but that the prolapsed gravid uterus should be manually replaced and supported by a pessary. As an adjunct to early rising in the puerperium, it has been recommended that a suitable pessary be inserted immediately after vaginal delivery. Pelvic examination at 6 weeks postpartum reveals from 20 to 30 per cent of uteri to be in retroposition. The advisability of replacing the uterus and inserting a suitable pessary is clearly seen. The earlier this is done in the puerperium the greater the chance of avoiding permanent retrodisplacement.

Gynecological indications for the use of a pessary include sterility associated with retrodisplaced uterus, for a therapeutic test prior to uterine suspension in patients thought to be presenting symptomatic retropositions, and immediately after suspension operations in order to relieve the strain upon the shortened uterine ligaments and thus facilitate healing. Vaginal pessaries continue to be useful for temporary support of a prolapsed uterovaginal tract while the patient is being prepared for corrective surgery. Prolapse of the ovary with an associated retrodisplacement of the uterus is usually attended by prompt and often lasting relief after the insertion of a Smith-Hodge pessary, worn for several weeks. In primary dysmenorrhea, particularly in the nulliparous young woman with a hypoplastic uterus, thorough dilatation of the cervix followed by the insertion of a stem pessary may be helpful.

The author outlines various abuses of the pessary. Patients should not have to wear pessaries for an indefinite period of time. Pessaries should not be used in women suffering from acute or subacute pelvic infections. The employment of stem pessaries for more than 6 months is contraindicated and the use of a stem pessary for contraceptive purposes is reprehensible. Without first correcting the retrodisplacement, the insertion of a pessary is an irrational gesture, and instances of "fixed" or adherent retroversion cannot be benefited with a pessary. Wearing a pessary should not be attended by discomfort to the patient. The patient should be followed at regular intervals while wearing a pessary, and the latter should be removed by the physician at regular intervals for inspection of the vaginal mucosa.

The writer discusses the various types of pessaries and the situations in which each is particularly useful. The proper technic of pessary application is described. 5 figures.

THE ADNEXA

CYSTIC TERATOMA (DERMOID CYST) OF THE OVARY; A STUDY OF FIFTY-TWO CASES

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The authors have made a clinico-pathological study of cystic teratoma in the laboratory of this hospital, which is purely for Negro patients. A total of 52 cases of cystic teratoma of the ovary was encountered over a period of 24 years. During this time, 1,920 cases were studied, with the finding of 87 tumors, the percentage of cystic teratoma therefore being 59.77 per cent.

The majority of cases occurred between the ages of 21 and 40 years. Eight per cent of the tumors were bilateral. The size of the tumors ranged from about 1 cm. to that of a combined multilocular serous cyst and dermoid cyst of tremendous size, 40 by 30 by 21 cm., weighing 11,820 gms. Symptomatology was considerably varied, although the most frequent complaint was a mass in the lower abdomen with associated pain, usually of short duration. The fact that many of the dermoid findings are asymptomatic would suggest the possibility that painful growths might be caused by other existing pathology.

In this study, the most frequent extra-ovarian complications were 22 cases of salpingitis, 15 cases of leiomyofibroma of the uterus and 5 cases of appendicitis. Pregnancy was another complication, of which one led to cesarean section and another came to autopsy, at which time the diagnosis of ruptured dermoid cyst was made with a consequent diffuse peritonitis as the cause of death. The contents of the tumor are very irritating and may cause peritonitis; it is for this reason that aspiration of the tumor is contraindicated.

Among the many tissues recognized in the writers' collection of cystic teratoma, one is particularly stressed because of its rarity, namely, parathyroid. This tissue was found in combination with 13 other structures in the same ovary. There were no recognized malignancies.

Because of the variety of structures from the 3 primary germ layers included in the ovaries, the authors suggest that the name cystic teratoma of the ovary should not be despised; rather it should take precedence over the timeworn term, dermoid cyst. Inasmuch as the tumor is grossly recognized by the more frequent components such as skin, lipoid, hair, bone and teeth, the presence of many of the less spectacular tissues that further characterize the tumor should be given consideration, until ruled out by microscopic examination.

Without considering the possible subclinical existence of the disease, patho-

worm and ova encapsulated in a lymph node on the round ligament has not previously been noted.

A 26-year-old woman was admitted to the hospital about 3 months after her third delivery for repair of a rectocele and exploration of the pelvis because of lower abdominal discomfort with sense of pressure and enlargement of a pelvic mass. At operation a large benign serous cystadenoma of the left ovary was found and the left tube and ovary and appendix were removed. On the left round ligament a nodule, 8 mm. in diameter, was discovered not far from its uterine end. It was removed, and proved to be a lymph node within which a gravid female *Oxyuris vermicularis* and ova were encapsulated. Later questioning revealed no history suggestive of infestation with the nematode. The patient recovered uneventfully.

The route by which the worm reached its final resting place is open to speculation. The rich lymphatic supply from the Fallopian tubes and uterus to the round ligaments makes it interesting to postulate a direct route from the uterus, but the size of the adult worm (cross section 500 by 600 microns) would seem to make this route an impossibility. However, since worms and ova have been found in the genital tract and peritoneal cavity, this route is not beyond the realm of possibility. 2 figures.

tissue. There was diffuse infiltration and focal collections with lymphocytes. There was also a tendency of cells to form fasciculi. Some areas showed extensive necrosis. In another section there was capillary dilatation and focal hemorrhage. Here the tumor was more cellular and the cells were embryonic in type. The histologic findings were similar to those described by Meyer as characteristic of dysgerminoma.

The patient was given a course of deep x-ray therapy postoperatively, but she did not improve and died approximately 3 months after operation.

(When a solid ovarian tumor is encountered in a child or a young woman, one should always think of the probability of its being a dysgerminoma. The rare teratomas which may be encountered have a very different gross appearance, while granulosa cell tumors in prepubertal patients are characterized by precocious sex puberty changes, which are lacking in dysgerminoma.

While the entire so-called dysontogenetic group of tumors, comprising granulosa cell tumor and thecoma, dysgerminoma and arrhenoblastoma, are as a group much less malignant than the common types of primary ovarian carcinoma, it is my feeling that they are spoken of much too lightly by many authors, and that they all possess a potential malignancy, which all too frequently becomes very real. More and more cases of recurrence and metastasis, with fatal termination, are appearing in the literature. It is in such problems as this that the follow-up study of the material being accumulated by the Ovarian Tumor Registry may yield valuable information within the next few years.—Ed.)

GRANULOSA CELL TUMOR OF THE OVARY

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Granulosa cell tumor comprises about 10 per cent of all solid malignant ovarian tumors. The majority of cases develop between the ages of 30 and 50 years; less than 10 per cent occur before puberty, and 30 per cent after the menopause. At the authors' hospital this tumor has been seen but twice in the last 25 years, despite the fact that the tumor has been sought diligently in the pathological material which has passed through the laboratories.

The 2 case reports are presented, the first patient being 45 years old, the second, 36 years old. Neither of these cases was diagnosed except by the histological examination. This was probably due to the fact that the hyperestrogenism occurred while these patients were still having full active ovarian function. Granulosa cell tumors occurring in the adult age period do not present striking symptoms.

The 2 cases illustrate the extremes which these tumors may present in the matter of malignancy. In the first case the tumor was highly anaplastic and clinically malignant. Bilateral salpingo-oophorectomy and supravaginal hys-

logical study of this small collection of cases would connote a very high incidence of cystic teratoma of the ovary in Negroes. 7 figures.

(It is quite certain that the term cystic teratoma will not dislodge the designation of dermoid for the tumors in question, even though it may have some theoretical advantages, any more than gynecologists are going to stop speaking of uterine myomas as fibroids. By this I mean that the way of the reformer in medical nomenclature is a rather hard one, and long usage is apt to prove a stronger force than scientific precision. It is true that a dermoid is a cystic teratoma, but there are other differences between dermoids and teratomas, as the terms are used.

The most important of these lies in the fact that the dermoid is a benign tumor, and the solid teratoma a malignant one. The fact that the latter is made up of a jumble of elements derived from all three fetal layers is probably not the complete answer, for the dermoid is not by any means always purely ectodermal, though ectodermal structures are the dominating ones. The difference must lie in the immaturity of the teratomatous elements, and this may even be evident histologically. One reason why even a good histologist may find difficulty in identifying all the elements of a complex teratoma lies in the fact that they are often present in embryonic and therefore not easily differentiable form. It is easy to believe that this unripe embryonic tissue would be more likely to assume malignant characteristics than would, for example, the well-differentiated mature skin and skin appendages characterizing the ordinary dermoid cyst.—Ed.)

DYSGERMINOMA OF THE OVARY IN A 7-YEAR-OLD CHILD

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A 7-year-old girl was admitted to the hospital with the complaint of fever, nausea and vomiting, and pains in the abdomen of several days' duration. Examination revealed a symmetrically distended abdomen with a large, somewhat nodular tumor filling the entire abdomen from the symphysis pubis to the xiphoid process. Rectal examination revealed that the lower pole of the tumor extended deep into the cul-de-sac, was somewhat tender and apparently well fixed.

At operation, a solid tumor was found which extended from the pelvis almost to the xiphoid process. The tumor was freed by sharp and blunt dissection. The tumor could be seen to arise from the left ovary, was lobulated, rather rubbery in consistency, grayish in appearance and there were numerous hemorrhagic areas over the posterior surface. The mass was solid without evidence of cystic degeneration. Supravaginal hysterectomy and bilateral salpingo-oophorectomy were done.

Microscopically, the bulk of tissue consisted of rather pleomorphic medium-sized to large tumor cells with oval or round hyperchromatic nuclei and abundant acidophilic cytoplasm. Cellular areas alternated with rarified myxomatous

report a case of carcinomatous degeneration of Brenner's tumor which would seem to justify further study of the nature of this growth.

The case was that of a woman 70 years old who had been suffering from a slight bloody discharge for two years. When admitted to the Women's Clinic at the University of Gottingen she complained of vague abdominal pains and swelling. The gynecological examination showed a moderate abdominal dropsy. A compact movable tumor could be felt in the left lower abdomen, while the right adnexal region was free. The uterus was somewhat enlarged and dextroposed. Following the diagnosis of a malignant growth arising in the left ovary the tumor was removed after the drainage of 3000 cc. of serous fluid from the abdominal cavity.

The tumor measured 13 x 15 x 17 cm. The surface was coarse, nodulated and enclosed in a serous sac. On one side ran the excised tube. The consistency of the growth was partly solid, partly cystic, and the solid sections were predominantly fibrous, gray-white in color. There were a number of irregularly distributed small cysts, and a pithy area the size of a 25-cent piece. Nearby was a spongy area of the same dimensions. The walls of the larger cavities were 3–6 cm. thick and contained small daughter cysts. The inner surfaces of the larger cysts were mostly smooth, with here and there a thickening of the outer covering. The wall of one of the larger cysts was pithy in spots.

A microscopic examination of the fibrous portion of the tumor revealed a number of irregularly distributed undifferentiated epithelial nests embedded in connective tissue which was markedly hyalinized and calcified in spots. They contained small cavities visible to the naked eye. These were of three types: cysts covered by a many layered neutral epithelium, cysts in which only the basic epithelial cells had kept their neutral character and whose inner layers were composed of walled up cells with a positive mucicarmine coloring, and cysts whose inner rows of cells had been transformed into a mucicarmine positive cylindrical epithelium.

The pulpy part of the tumor consisted of a large carcinomatous epithelial mass transversed by narrow strips of connective tissue formed predominantly of polygonal cells with wide atypical variations including giant cells. Some of these cells had preserved their neutral character.

The spongy area was full of cavities with an unmistakably malignant, many layered atypical mucicarmine-negative epithelium, showing a direct transition from the solid benign epithelial nests. The epithelial coating of the larger cysts was very thick and displayed all the characteristics of a malignant tumor. The mucous membrane of the uterus showed a polypous hyperplasia.

On the basis of the histological examination in the above case, the tumor was diagnosed as a solid Brenner's tumor with a cystlike formation containing likewise carcinomatous growths. It was observed, however, that the carcinomatous parts of the solid and cystlike sections alike sprang from the local tissue, that they showed different morphological structures and therefore it was to be assumed that the malignant degeneracy of both parts developed independently.

As is well known, the Brenner tumor consists of two parts, the parenchyma

terectomy were performed.   One month after operation, follow-up examination revealed extensive metastasis to the lungs.   In the second case the tumor was histologically benign.   Six months after operation (left salpingo-oophorectomy, supravaginal hysterectomy), the pelvis was clear and there was no evidence of recurrence or spread.   4 figures.

(Granulosa cell carcinoma, as pathologists have become more and more familiar with its microscopic characteristics, has become anything but a rare tumor type.   In our own laboratory, for example, I would say that we have sections from at least 200 cases, although the overwhelming majority of these were sent in for diagnosis from various outside sources.

Both of the cases reported by the authors occurred in patients during the reproductive period of life, and it is therefore not surprising that there were no distinct manifestations of the estrogen-producing capacities of such tumors.   The only effects produced at this age epoch would be a hyperestrogenism, and these may be negligible.   Menstruation may be essentially normal, it may be somewhat excessive, or irregular, or there may be long periods of amenorrhea, variations which one might expect in women subjected to a quantitative increase in estrogen.

It is in the prepubertal child, at a period in which there is ordinarily little or no estrogen, that the most spectacular results are seen from the presence of an estrogen-producing tumor. It is estrogen which produces the striking secondary sex character changes which characterize normal puberty.   The abnormally early subjection of the child to a similar estrogen influence when this is produced by a granulosa cell tumor brings about precocious puberty, with menstruation-like bleeding, mammary development, axillary and genital hair, and abnormal development of both the uterus and the external genitalia.   All these symptoms quickly disappear after removal of the tumor.

It is well to remember that the precocious menstruation in such cases is purely estrogen-induced, i.e., it is not accompanied by ovulation.   In this respect this variety of precocious puberty differs from the more common constitutional type, in which both menstruation and ovulation occur abnormally early.   In the latter form pregnancy may occur if the child is inseminated, and it is this type of precocious puberty which explains the cases of pregnancy at abnormally early ages, as in that of Lena Medina, the youngest mother in the history of the race.   It will be recalled that this little Peruvian girl was delivered of a full term baby by cesarean section at the age of 5½ years.

When granulosal or thecomatous tumors occur in women beyond the menopause, the senile uterus is reconverted to a size like that seen in the reproductive epoch, and a periodic menstruation-like bleeding of estrogen induced type is observed.—Ed.)

IS BRENNER'S TUMOR ALWAYS A BENIGN GROWTH?

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The present paper constitutes a challenge to the generally accepted theory that the ovarian growth christened "Folliculoma Ovarii" by Brenner and commonly known as Brenner's tumor is invariably a benign growth.   The authors

that in a small minority of cases the squamous epithelium of a Brenner tumor may undergo pseudomucinous transformation, and that a very small fraction of pseudomucinous cystadenomas may arise in this fashion. There would seem to be no reason why malignant change should not in rare cases occur in pseudomucinous cysts of Brenner origin, as they not so rarely arise in the ordinary pseudomucinous cysts, which are commonly thought to be of teratomatous origin. The case reported is the first of its kind, but the fact still remains that the ordinary solid types of Brenner tumor are both histologically and clinically bengin.—Ed.)

A CASE OF SEROUS ADENOFIBROMA OF THE OVARY

A. Sharman and A. M. Sutherland

Royal Samaritan Hospital for Women, Glasgow

J. Obst. & Gynaec. Brit. Emp., 54: 382–383, 1947

Serous adenofibroma is one of the rarest of all ovarian tumors. Scott has reviewed the case reports of ovarian tumors in the files of the Johns Hopkins Hospital, embracing a total of 26,000 gynecological cases, and found 13 reports of such tumors together with one report found in the general pathology files. Scott divides these tumors into 2 groups; in his series there were 8 adenofibromas and 8 cystadenofibromas, bilateral tumors being found in 2 patients.

The authors report the case of a 56-year-old woman who complained of vaginal bleeding of 2 months' duration, beginning 11 years after the menopause. A large firm abdominal tumor was found on examination. Operation revealed that the mass was a solid tumor of the left ovary. Left ovariotomy and resection of a portion of the right ovary were performed.

Microscopic examination of the ovarian tumor revealed 2 constituent elements, namely, a fibromatous stroma and a large number of gland-like or cystic spaces of varying size. In some places tiny papillary projections into the cyst spaces were seen. The spaces were lined by columnar, cubical or flattened epithelium, which was compactly arranged, usually in a single layer, with centrally placed nuclei. No evidence of malignancy was found. The attached Fallopian tube was elongated but otherwise normal.

When seen 10 months after operation, the patient had remained well with no recurrence of vaginal bleeding. The cervix and uterine body were found to be atrophic. 3 figures.

(This neoplastic form is relatively uncommon, as the author states. While usually of small size, such tumors may become quite large, as in the authors' case, or in one which I encountered a year or so ago. In this latter case the tumor was a bilateral one, each ovary being replaced by a tumor about twice the size of a normal kidney, and not unlike the latter in shape. Such tumors are not easy to distinguish grossly from carcinoma, and in my own case, the preliminary impression at operation was that we had to deal with a bilateral carcinoma. It was not until the tumors were opened, revealing a mixture of solid fibromatous

and the stroma. As they are equally important it is necessary to take this fact into account in the study of its histogenesis. One theory as to its origin is that it develops in granulosa cells, but this can be at once discarded, as tumors having such an origin exhibit signs of follicular hormone activity which has not been found in Brenner's tumors up to the present time.

Another possibility is that the tumor originates in the so-called Walthard islets. This theory would seem to be well founded, as the superficial epithelium is derived from the celomic epithelium, which is able to produce mucous, serous and pavement epithelium. However, some authorities suggest that the ovarian rete in which Brenner epithelial-like formations have been found may be the source of the Brenner epithelium.

The authors of the present paper advance the theory that the Brenner epithelium may have its origin in latent embryonic remains, remarking that ovarian and extraovarian Brenner epithelial-like islands often show no relation to the superficial epithelium as far as the ovarian rete is concerned. These embryonic remains must exist in tissues which have the generative powers existing only in the celomic epithelium. However, as the latter cannot form connective tissue, the parenchyma and the stroma have no common matrix, and it is therefore to be concluded, if we accept this theory, that the stroma is derived from the connective tissue surrounding the epithelial segments.

A genetic classification of Brenner tumors places them in the same category with other benign ovarian tumors, beginning with the Walthard nodules from which tumors may develop. Next come the so-called cyst-like Brenner tumors, then cystomas with marginal nodules of Brenner's tumor, and finally serous pseudomucinous or mixed cystomas.

The tumor studied by the authors exhibited all the characteristics of the types described above, combined with a malignant degeneration producing a carcinomatous growth similar to a cystic adenocarcinoma. Their observations led them to question whether the case in point was an exceptional occurrence or whether ovarian carcinomas may develop from Brenner's tumors without their origin being suspected.

They conclude their paper with the observation that cyclic abnormalities such as metrorrhagic hemorrhages are often found in conjunction with Brenner's tumor, as well as with hyperplastic changes in the mucous membrane of the uterus, both observed in the case described. They discount the theory of hormonal influence as it could not be demonstrated in 280 or more cases on record, but they believe that hormonal examinations, supplementing morphological examinations, might provide an authoritative answer to this question.

(As far as I know, every case of Brenner tumor heretofore reported has been clinically benign with one possible exception in the case reported by a Russian author many years ago in an inaccessible Russian journal. The circumstances of this case, as gleaned from available abstracts, suggested that it represented only a bilateral but benign Brenner tumor and not a recurrence, as suspected by the author.

The case reported by the authors would seem to be, on the basis of the microscopic description and the rather poor photomicrographs accompanying the paper, a pseudomucinous cystadenocarcinoma arising, at least indirectly, from a Brenner tumor. It is well known

that in a small minority of cases the squamous epithelium of a Brenner tumor may undergo pseudomucinous transformation, and that a very small fraction of pseudomucinous cystadenomas may arise in this fashion. There would seem to be no reason why malignant change should not in rare cases occur in pseudomucinous cysts of Brenner origin, as they not so rarely arise in the ordinary pseudomucinous cysts, which are commonly thought to be of teratomatous origin. The case reported is the first of its kind, but the fact still remains that the ordinary solid types of Brenner tumor are both histologically and clinically bengin.—Ed.)

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looking areas and many small cysts, that one could be reasonably sure of its nature. The microscopic appearance was like that described in the authors' case, of which I also had the opportunity of studying sections, through the kindness of Dr. Sharman. Both clinically and microscopically, such tumors are of course benign.—Ed.)

CEROID IN THE HUMAN OVARY, WITH SPECIAL REFERENCE TO ITS MODE OF FORMATION

S. Brenner

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While conducting a routine survey of human tissues with the fluorescent microscope, attention was drawn to the presence of a number of globules in the human ovary which gave an intense yellow-white fluorescence. This led the author to suspect that the globules were ceroid.

Ceroid is a lipoidal pigment having the remarkable property of being highly insoluble in the usual fat solvents. Most of the earlier studies were confined to the pigment in experimentally produced hepatic cirrhosis in rats. More recent work has shown that ceroid is also found in the macrophages of the lung, spleen, bone marrow and lymph nodes as well as in the cortical cells of the adrenal gland.

By using the tests advocated by previous investigators, the author has shown that the yellow lipoidal pigment in the human ovary is ceroid.

It is suggested that the luteolipin in macaque ovaries is probably identical with ceroid.

The formation of ceroid is briefly discussed in relation to the enzyme lipoxidase, unsaturated fatty acids and vitamins A and E.

THE EFFECT OF PROLAPSE OF THE OVARIES UPON CYSTIC DEGENERATION AND OVULATION

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Polycystic disease of the ovaries is an infrequently recognized clinical entity. Various etiologic theories have been proposed, the current theories explaining

this condition on the basis of a hormonal dysfunction. The influence of circulatory impairment has been suggested both experimentally and clinically. Butcher demonstrated experimentally by means of ligation that the germ cells have little resistance and soon perish. In all ligation experiments the more mature follicles withstood partial impairment of the circulation more satisfactorily. The hyperemia noted in polycystic ovaries has been listed by several writers as one of the probable causes of cystic degeneration, with the congestion a factor in increased follicular activity.

To test the theory that polycystic disease of the ovaries is the result of impaired circulation to the ovaries, primarily due to the congestion following prolapse of these organs, such a condition was artificially produced in rabbits and dogs. It was found that circulatory impairment by artificial prolapse of the ovaries in rabbits causes follicular atresia. Seven of 8 rabbits with artificially prolapsed ovaries did not become pregnant, although they were mated with normal bucks.

The authors suggest that polycystic disease of the ovaries is produced by follicular atresia resulting from persistent vascular congestion, and that follicular atresia is the result of faulty nutrition to the ovum of vesicular follicles. The treatment of polycystic disease of the ovaries is directed toward improving the circulation by partial resection and suspension of the ovary. The release of tension within the ovary which is produced by partial resection immediately improves the circulatory status of the gland, inviting a return to normal function. The authors tabulate 13 cases of polycystic disease and report in detail one case demonstrating a normal hormonal balance. 3 figures.

(The opening sentence of this abstract indicates the changed attitude toward cystic ovaries, as contrasted with that of a former day, when such a diagnosis was frequently made and, unfortunately, was considered an indication for removal of such ovaries. The so-called Battey operation (this is not a pun) was at one time widely done, the cystic ovary being blamed for all manner of female ailments, such as nervousness, headache and epilepsy. As the authors state, polycystic disease of the ovaries is not often recognized as a clinical entity nowadays, and I know of no good evidence that the present conservative attitude of gynecologists on this subject is not fully justified.

Certainly one sees many cystic ovaries which are not prolapsed, and other factors are undoubtedly often concerned in the exaggerated follicle atresia which is concerned in such cases. The cause is quite surely not always the same. Some cases are of hormonal origin, the ovarian cystic change being a secondary and unimportant manifestation of what is usually a pituitary gonadotrophic dysfunction. A good example of this is seen in the cystic change which is often seen in the residual ovarian tissue after removal of one ovary and resection of the other. Such cystic changes were formerly attributed entirely to circulatory disturbance, but the probable explanation, based on the "law of follicle constancy of Lipschutz" is that they are explained by the concentration of a constant pituitary gonadotrophic stimulus upon a reduced ovarian surface. Perhaps a better example is the polycystic ovary seen in at least one considerable group of cases of functional bleeding of the anovulatory type (metropathia hemorrhagica), and unquestionably only a reflection of the underlying pituitary dysfunction.

It is quite possible, or even probable, that circulatory disturbances, whether in the direction of deficiency of blood supply or in the persistent vascular congestion which the authors emphasize, may at times be concerned. The subject is still too hazy to justify any

very emphatic opinions.   Incidentally, the cystic ovaries which one so often sees at oper-
ations for other indications are often associated with no menstrual or other symptoms which
could be intelligently referred to them.   In most cases they can be disregarded unless the
ovaries are grossly greatly enlarged, so that they may appear to explain such symptoms as
heaviness or bearing down.   Under such conditions resection, with or without suspension,
would be rational.   Needling of the larger cystic follicles may hasten their involution.

While resection of the ovaries is certainly a proper procedure in some cases, it would be
most unwise to recommend it as a routine procedure just because they are "cystic," nor do
I believe that the authors have any such idea themselves.   In spite of care in technique, re-
section of the ovaries may be followed by such sequelae as intestinal adhesions or angulation
of the tubes.   I feel sure that every gynecologist has seen instances of this sort.   The old
dictum of "either take an ovary out completely or leave it alone" cannot be taken too
literally or inflexibly, but there is much sense behind the general idea.—Ed.)

A CASE OF PRIMARY TUBAL CARCINOMA

G. LUCKHAUS

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Primary tubal carcinoma is a relatively rare form of tumor.   According to
the latest statistics about 390 cases have been recorded.   Clinical symptoms of
the disease are few, among them being leukorrhea, hydrops of the tube and ir-
regular bleeding.   However, such symptoms are unreliable and may be com-
pletely lacking.   The carcinoma frequently has the form of an adnexal tumor
shaped like a sausage or postillion's horn, and is of cyst-like consistency, such
as may be found in a hydro- or pyosalpinx.

The prognosis is 4 per cent permanent cure at the highest, and therapeutically
involves the total extirpation of the uterus and adnexa, together with roentgen
ray treatments.   Histologically, it usually takes the form of a cylindrical epi-
thelial *carcinoma of the papillary alveolar type*, which spreads either through
the lymph passages into the glands along the aorta and canalicularly into the
cavum uteri, or by infiltration of the neighboring organs after breaking through
the wall of the tube.

As to the etiology of primary tubal carcinoma there are two different opinions.
One view is that it always develops on the seat of chronic salpingitis.   In de-
fense of this theory the many histologically demonstrable chronic inflammatory
changes in the tubes are cited, as well as the marked preponderance of tubal
carcinoma in sterile women.

On the other hand, many authorities stress the fact that many cases of tubal
carcinoma are unaccompanied by salpingitis.   They stress also its *rarity* in
comparison with the frequency of salpingitis, and the unilateral character of
the carcinoma as contrasted with the bilateral character of inflammatory ad-
nexal tumors.

Judging by the case reports published so far, both possibilities as to the origin of tubal carcinoma must be considered. As an example, the author contributes the following report of a case which came under his observation.

Mrs. C., 49 years old, was admitted to the Women's Clinic of the Municipal Hospital at Remschied, Germany, on account of severe stabbing pains in the right hypogastrium, which lasted for 2 days and then disappeared.

Her mother had died of carcinoma of the liver. Her general health had always been excellent, her marriage childless. Some months previously she underwent a curettage to relieve climacteric hemorrhages, but no other abnormal conditions were observed except a loss in weight which amounted to 5 kilos in 6 months.

When she was admitted to the hospital her general condition was good. Pelvic examination revealed the fact that behind the anteverted uterus there was a broad-based tumor the size of a small apple, which took on poorly defined contours towards the rectum. The existence of a subserous myoma or an ovarian tumor was suspected.

Laparotomy resulted in the discovery of a twisted reddish-blue sausage shaped tube of cyst-like consistency and the size of a large hen's egg. There were extensive adhesions to the left ovary, the real wall of the uterus and the sigmoid. The right ovary had degenerated and was filled with small cysts, while the right tube was inflamed and of the thickness of a lead pencil, the abdominal ostium closed.

On the assumption that he was dealing with a hydrosalpinx, the operator excised the left adnexa after loosening the adhesions, and performed a ⅔ excision of the right ovary.

When the tube was opened after the operation the interior was found to be clogged with a pulpy yellow mass leading to the suspicion of the existence of a tubal carcinoma, later confirmed by histological examination.

Consequently, another laparotomy with total removal of the uterus and its right adnexa was performed several weeks later. Some enlarged lymphatic glands could be felt along the left iliac blood vessels, in the hollow of the sacrum to the left of the median line and on the promontory at the departure of the iliac artery from the aorta. Several lymphatic glands were removed.

Histologically the picture was that of a cystically distended tube full of atypical epithelial tumorous tissue preponderantly solid in growth, and many atypical mitoses with marked cell polymorphism. The tumorous tissue was cylindro-cellular, containing here and there remains of mucous papules.

The tumor was limited to the inner lining of the tube. Examination of the uterus and the right adnexa showed no abnormality except chronic inflammation. The lymphatic glands when examined showed only a chronic lymphadenitis. Nearby in the uterine wall was an intramural myoma the size of a pea.

The final diagnosis was that of a preponderantly papillary tubal carcinoma together with a nonspecific chronic salpingitis and a left-sided hydrosalpinx.

(The clinical history of this case, as well as the operative and microscopic findings, are quite typical of the rare primary tubal carcinoma. The only symptom, and this may be a

late one, is likely to be a postmenopausal bleeding, although Luckhaus' patient also had pain. However, this was on the right, while the tumor was on the left, and the pain was quite surely due to the right-sided adnexitis. Most cases, as encountered at operation, show a sausage-like tube which looks like a big pyosalpinx, but often differs from the latter in being free or almost free of adhesions. This, however, is the picture of a late stage, while the occasional earlier cases which have been observed show only a small localized mass in some portion of the wall of an otherwise normal tube, or one the seat of a chronic salpingitis or hydrosalpinx. The earliest case in the literature is that reported by Mitchell and Mohler in 1945 (See Survey, 1:127, 1946). In this case the routine examination of a small loop of an apparently normal tube which was resected for sterilization purposes showed, as a purely accidental but lucky find, a beginning but very definite papillary carcinoma. I had the opportunity of studying the sections of this case through the kindness of Dr. Mohler. The patient has remained well for about 3 years after operation, and the prospects for permanent cure seem excellent.

The common microscopic pattern is that of a very papillary growth which pushes into the lumen from the mucosa, so that in late stages the lumen is distended with this papillary growth, with characteristically no tendency to infiltrate the deeper tubal layers. Variations of this pattern may occasionally produce the so-called papillary alveolar type.—Ed.)

MEDICAL VERSUS SURGICAL TREATMENT OF PELVIC INFLAMMATORY DISEASE

R. B. WILSON

Mayo Clinic

Surg. Clin. North America, 27: 866–874, 1947

The author re-emphasizes the fact that the medical and surgical treatments of pelvic inflammatory disease are to be used to complement each other. It is felt that all patients suffering from such disease should first receive conservative medical management. Medical treatment is the treatment of choice in the acute case; on the other hand, the patient with large adnexal masses, who gives a long-standing history of repeated flare-ups and who has disabling symptoms is hardly a candidate for medical treatment.

Early and adequate medical treatment by our present-day methods should cause a marked decrease in the number of instances in which surgical intervention is required. If possible, therapy should be started when the infectious process is limited to the urethra and cervix in the gonorrheal type of infection and when the very first sign of visceral involvement occurs in other types of infection. Certainly a good end result, with salvage of the reproductive function, will hinge to a great extent on such early and adequate treatment. Such treatment will often effect a clinical cure; in those cases in which cure does not take place after such treatment, the patient will be in better condition to undergo operation.

The procedures in medical treatment may be divided into 3 categories: (1) General and supportive measures; the need for these varies with the severity of

the disease. Severe cases will require parenteral administration of adequate amounts of fluids, sedation, bed rest and correction of any aberrations in blood chemistry. (2) Sulfonamides or penicillin should be administered to all patients exhibiting evidence of acute infection. Early treatment of both specific and non-specific infections is most important; this is particularly true in gonorrheal urethritis and cervicitis. (3) Diathermy is considered to be one of the most effective measures in the elimination of pelvic inflammatory disease and its residua. The only contraindication to pelvic diathermy is vaginal bleeding.

Only after trial of such a course of medical therapy should surgical treatment be considered. In general, pelvic operation should not be performed in the presence of fever or an elevated leucocyte count. The patient's general condition should be improved as much as possible prior to operation. Ovarian function should be preserved, when possible, in women of 40 or under.

Four case reports are presented.

(The author's thesis, which few would dispute, is that surgery is practically never indicated because of existing pelvic infection, but that it is not infrequently still necessary because of the pathologic sequelae of such infection. An exception to the above generalization would be the acute pelvic abscess which may call for simple vaginal drainage. A chronic salpingitis matted with tl e ovary to adjoining structures, a large tuboovarian abscess, or a bilateral hydrosalpinx is commonly associated with no existing infection, and yet it may give rise to so much dysmenorrhea and lower abdominal pain as to call for surgical relief. Such lesions represent the wreckage left by an infectious storm which had swept over the adnexa perhaps many months or years previously.

On the other hand, there are innumerable women with chronic adnexal disease who have little or no symptomatology and who can go through life very comfortably without operation. Other considerations, such as sterility, may at times project themselves into the evaluation of these cases, but a large proportion can be treated expectantly or with simple palliative measures.—Ed.)

OPERATIVE GYNECOLOGY

SURGICAL TREATMENT OF ACUTE GYNECOLOGIC CONDITIONS

J. H. PRATT

Mayo Clinic

Of 727 emergency operations performed during 1945 and 1946 at the Clinic, 117 (16.1 per cent) were gynecologic. In 55 cases there were vaginal symptoms requiring dilatation and curettage alone. Of these 55 cases, 43 (36.8 per cent) were of incomplete abortion. In 18 cases (15.4 per cent) ectopic pregnancies were operated on without a death. Bleeding from a graafian follicle or a corpus luteum was the reason for 17 (14.5 per cent) operations while 7 patients (6.0 per cent) had acute torsion of an ovary or tube. The remaining 20 cases (17.1 per cent) comprised ruptured endometrial cysts, pelvic abscesses, acute salpingitis, ruptured uterus, etc. In the 2 most important groups there has been a lowering of mortality and morbidity rates in recent years. In the incomplete abortions it has been due to chemotherapy as well as to supportive treatment. In ectopic pregnancy the mortality rate depends entirely on early treatment and preoperative and postoperative care with attention in particular to the restoration of the circulating blood volume.

The cases of congenital lesions that fall into the realm of acute surgical conditions generally present the history of a girl in her teens who has never menstruated but has for some time had pains at monthly intervals. Hematocolpos or hematometra may be diagnosed; in either case the surgeon must furnish an outlet for the menstrual blood and preserve as normal a genital tract as possible. A variation of this type of lesion occurs when there is duplication of the genital tract. In the case of a doubling of part of the vagina the intervening wall can be excised and care taken that adhesions do not form in the vagina postoperatively. If there is a double uterus with one side functioning normally and the second with no external opening, partial hysterectomy of the malformed segment is necessary.

The abdominal emergencies are the most serious of the acute gynecologic emergencies. Ectopic pregnancy is outstanding of all the abdominal conditions. In a study of 101 deaths from ectopic pregnancy in Philadelphia from 1931 to 1943, it was found that delay in diagnosis, insufficient attention to preoperative and postoperative care and inadequate transfusions were the chief factors in the failures.

Usually the patient is seen in mild shock, pale and perspiring, with a distended, extremely tender abdomen and with marked rebound tenderness. The

temperature is low or subnormal, the pulse rapid and weak and the blood pressure low. Restlessness, particularly air hunger and dyspnea, is the most reliable sign as to the seriousness of the blood loss. Pelvic examination will show exquisite pain on any motion of the cervix. Suggestive signs of pregnancy should be looked for, such as softening of the cervix, etc. The history of typical cases will be of a very sudden onset of acute low abdominal pain, possibly causing fainting or collapse. The pain is continuous. The last menses may be absent of possibly delayed, but spotting may continue for days after a normal period would have ended. A history of intercourse is seldom difficult to obtain.

In cases of tubal abortion when the products of gestation are passing out of the fimbriated end of the tube, the bleeding and shock may not be so extreme. Granted that the patient is in good shape without much loss of blood as shown by the hemoglobin determination, as well as minimal abdominal findings, it is usually worthwhile to wait for confirmative reports from a Friedman test.

When a diagnosis of ectopic pregnancy has been made, the only treatment is operative. After opening the abdomen, salpingectomy can be done, preserving the ovary. If the patient is in fair condition the stump of the tube should be covered by the round ligament and the adnexa should be peritonealized. The opposite tube should always be inspected. All blood clots should be sponged out of the pelvis.

When the patient is in shock on admission she should be treated for shock while the operating room is being prepared. Intravenous administration of isotonic saline solution containing glucose should be started slowly through a large bore needle. If the patient is a multipara or gives a history of transfusions or multiple miscarriages, the Rh factor must be determined. No attempt should be made to raise the blood pressure to normal, as this will only provoke further hemorrhage, but enough fluids should be given preoperatively to keep the systolic pressure between 80 and 100 mm. Hg. The abdomen is opened in the midline, the uterus is identified, the tubes are quickly palpated and the one containing the pregnancy is tightly clamped between the fingers. With the bleeding thus controlled the blood clots can be evacuated. As soon as the vessels to the tube are clamped and the bleeding is controlled, transfusions are of the greatest benefit as they can now be used to build up the pressure and circulating volume without danger of further hemorrhage. The appendix is not disturbed and the incision is closed in layers. The author states that regardless of how bad the condition of these patients seems when they are first seen, accurate diagnosis with early surgical intervention and early restoration of the circulating blood volume will save practically all of them.

In cases of torsion of an ovarian cyst, the onset is typically sudden in more than half the cases, and rather gradual in the remainder. The pain is low abdominal and often unilateral. If it is referred down the thigh of the affected side, this fact is extremely helpful in diagnosis. Nausea and vomiting are frequent. Roentgenographic examination is often helpful.

Examination will reveal a tender lower abdominal wall, often with considerable rigidity. The majority of tumors that twist on their pedicles are large and

easily palpable. They can usually be easily delivered at operation and the pedicle divided between clamps. The remaining ovary must be inspected.

The symptoms of a twisted Fallopian tube are similar to those of torsion of a cyst but the physical findings are not as definite as when an ovarian tumor is encountered. Surgical treatment consists in excision of the affected tube with preservation of ovarian tissue if it is feasible.

"Mittelschmerz" is pain due to the rupture of a graafian follicle cyst at the time of ovulation with the spilling of a small amount of blood into the peritoneal cavity. It is encountered also in the third week of the cycle after a corpus luteum has formed. Mittelschmerz differs from appendicitis in being a low abdominal pain, sudden in onset, with maximal pain from the beginning and minimal, if any, temperature reaction. Tenderness is not marked and there is seldom real spasm or rigidity of the muscles. Mittelschmerz differs from ectopic pregnancy in the normality of the menstrual history, its characteristic midcycle occurrence, the lack of suggestive signs of pregnancy and the negative Friedman reaction.

If the diagnosis of mittelschmerz is made the treatment is conservative, with the patient kept under observation. When the diagnosis is in doubt between mittelschmerz and appendicitis it is best to carry out an exploratory laparotomy.

Acute salpingitis is now a medical disease in its early stages and should be treated by chemotherapy, adequate fluids and diet, rest and pelvic heat. It is primarily in the cases of early salpingitis, when the diagnosis is in doubt between acute salpingitis and appendicitis or mittelschmerz, that pelvic inflammatory disease enters the field of the acute surgical emergency. Pelvic inflammatory disease starts characteristically after some provocation or pelvic insult. The pain is bilateral and low in the pelvis with minimal abdominal spasm. The temperature is elevated often to 102 to 104 degrees F., with a marked elevation of leukocyte count and sedimentation rate. There may be evidence of acute infection in the glands about the introitus, in the vagina or in the cervix. On pelvic examination there will be marked tenderness on motion of the cervix with bilateral adnexal tenderness or masses. If the differential diagnosis of appendicitis cannot be satisfactorily made, exploration should be carried out at once. If acute salpingitis, even with purulent material dripping from the ends of the tubes, is encountered it should be left alone. Ten grams of sulfathiazole in the pelvis, plus postoperative chemotherapy, should resolve the infection with a good chance of preservation of function of the tubes.

Occasionally, ruptured endometrial cysts are encountered as emergency cases. The pain is similar to that of mittelschmerz and is in the lower part of the abdomen but without extension. Physical examination reveals a markedly tender cervix and uterosacral ligaments. Nodules may be palpable behind the uterus. Once the abdomen is opened the surgeon can make the diagnosis at once by the collapsed cyst and the characteristic chocolate-colored fluid in the pelvis. The only cure is excision of all ovarian tissue. Unless the situation has been discussed preoperatively, it is better to be conservative than radical in the case of a young patient.

Rupture of a capsular vein of a leiomyoma is a rare condition associated with

all the signs of intra-abdominal hemorrhage plus the presence of a large pelvic tumor. Treatment is exploration through a·lower midline incision followed by hysterectomy. Occasionally, during pregnancy a fibroid degenerates and requires emergency operation. Myomectomy should be carried out if operation is necessary with the expectancy that the pregnancy will continue.

Finally, the writer discusses vaginal emergencies. Cervical or endometrial polyps or pedunculated fibroids may twist on their pedicles or become infarcted from pressure as they pass through the cervix. The small polyps can be twisted off without much trouble or further symptoms. Treatment of a prolapsing fibroid consists in the delivery of the fibroid, morcellating it if necessary. In the presence of severe infection, hysterectomy, if indicated, should be delayed for 3 months.

If the presenting symptom is vaginal bleeding, the history is all-important. A fibrous hymen will often bleed considerably when torn, but bleeding is easily controlled by one or 2 sutures.

Vaginal bleeding from the cervix or uterus not associated with pregnancy is generally the result of a polyp and can be treated by dilatation and curettage and removal of the polyp. However, if the patient is more than 40 years of age, vaginal bleeding should arouse suspicion of carcinoma whether a polyp is present or not.

The largest single group of gynecologic emergencies is incomplete abortions. The abortion may be incomplete, complete or inevitable when the patient is first seen. If the hemorrhage is severe, supportive treatment with external heat, intravenously administered fluids, transfusions and so forth is started at once, and regardless of temperature or foul discharge the uterus should be emptied at once. Usually an intrauterine pack is left in place to control bleeding. Sulfathiazole is also left in the uterus and chemotherapy is begun postoperatively in the presence of infection.

When bleeding is only moderate, the patient is put to bed, kept warm and given sedatives and intravenous fluids. Oxytocics are administered at once. When the uterus is contracting, gentle pressure will help to expel the secundines. The patient is given 24 to 48 hours to complete the abortion. If it is not completed in that time, dilatation and curettage will be necessary and should be carried out.

Intravenous administration of fluids or blood is started preoperatively, depending on the amount of blood loss and the patient's blood pressure. Pentothal sodium (intravenously) is the anesthetic of choice. The uterine cavity should be explored with placental forceps and any pieces of loose tissue removed. The largest dull curet is then used to scrape out the cavity. When the uterine wall begins to regain tone the large sharp curet can be used. Pitressin or ergotrate can be used intravenously if the uterus is large or the bleeding brisk. The uterus is wiped out with a gauze strip and if bleeding continues it can be packed. Some preparation of ergot should be used postoperatively to stimulate uterine contraction.

(A rather long abstract of this paper is presented, simply because it gives an excellent and comprehensive report of the numerous acute gynecologic conditions which were encountered in one large clinic, and which occur also in all others.

As the author states, one of the most serious gynecologic emergencies is that of ectopic pregnancy, in that comparatively small cataclysmic group which is accompanied by massive intra-abdominal bleeding. This may even be fatal, especially in the comparatively rare interstitial variety. On the other hand, when treatment is not delayed, when transfusion is fully utilized, and when the operation is done expeditiously but not excitedly, there is no group of cases in which the results are more gratifying. Although I have operated upon a large number of cases, it has been a great many years since I saw a death from tubal pregnancy.

The author rightly urges prompt operation, with fluids and blood while the operating room is being prepared. Many of the older gynecologists will remember the bitter discussion, stretching over a number of years, following the late Hunter Robb's advocacy of deferring operation, often for days, until the patient had recovered from shock. This doctrine was preached on the basis of experiments on dogs, which, according to Robb, did not die even though the uterine arteries were cut and allowed to bleed into the abdomen. But many women have died of bleeding due to tubal pregnancy and the control of the bleeding vessels is the rational and surgical method of checking such bleeding, although always with full utilization of such vitally important adjuvants as transfusion.

As to torsion of ovarian cysts, or even normal tubes, the symptoms are often quite acute, but often much less severe, so that even very long delay in operation often occurs, as was emphasized in a paper abstracted and commented upon in a previous issue of the Survey (Kelberg, M. R. and Randall, J. H., Torsion of adnexal tumors and its relation to surgical emergency. Am. J. Obst. & Gynec., *52*:464, 1946. Abstract and comment in Survey, February, 1947, p. 94). The differentiation between simple "mittelschmerz," which, contrary to what the author states, is not always accompanied by intra-abdominal bleeding, and the cases of genuine and sometimes massive intra-abdominal bleeding of ovarian origin, is not always easy to make, especially in milder degrees of the latter condition. When the bleeding is really massive, with accompanying shock, the preoperative diagnosis is likely to be ruptured ectopic pregnancy.

Endometrial cysts undoubtedly frequently perforate, and in fact they were given the designation of "perforative cysts" by Sampson in one of his early papers. Usually, however, there are no symptoms of the usually minute perforations, which are sealed off by the peritoneal reaction in adjacent organs, usually the posterior surface of the uterus and broad ligament. Such small perforations, however, may well permit of spill of the contents and probably endometrium.

The only endometrial cysts which are likely to rupture with a loud bang, so to speak, and with the production of acute abdominal symptoms, are those which reach a large size simply because they do not previously undergo the tiny perforations. Such cysts are therefore less apt to be adherent than are most endometrial cysts, and they may become as big as an orange, which is very large for a cyst of this type. If they then rupture, symptoms occur, and they are most likely to be mistaken for a ruptured tubal pregnancy or, if on the right side, an acute appendicitis.

The various other acute conditions mentioned by the author, are discussed soundly, and the paper may be read with especial profit by hospital residents and internes.—Ed.)

PANHYSTERECTOMY AND SUBTOTAL HYSTERECTOMY: INDICATIONS AND TECHNIC

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Mayo Clinic

Surg. Clin. North America, 27: 790–795, 1947

· The most common conditions which necessitate panhysterectomy are uterine fibroids concomitant with disease of the cervix, carcinoma of the uterine fundus, chronic pelvic inflammatory disease, ovarian malignant lesions and, sometimes, disseminated endometriosis.

The indications for performing panhysterectomy in cases of uterine fibroids should not be set forth rigidly. The crux of this argument is logically the pathologic condition of the cervix. The external os may appear normal and active endocervicitis may be overlooked. A cervix which appears grossly normal often becomes a source of infection after subtotal hysterectomy as a result of interference with its normal blood supply. For these reasons it becomes difficult to determine what patients should be treated by subtotal hysterectomy. The writer states that, regardless of the opposing views, it would seem that the interests of the young married woman would be better served if the cervix were left in position if it appears normal, history of infection is not obtained and she has not borne children. In cases of metritis and chronic inflammatory disease in which considerable edema is encountered in the ovarian ligaments and broad ligaments, total abdominal hysterectomy with removal of both adnexa is the safest procedure. In addition to the pathologic condition of the cervix, one other factor makes total abdominal hysterectomy preferable, particularly in parous women, and that is mobility of the cervix. In most women who have borne children considerable stretching and tearing of the pelvic muscles and fascia has occurred which is not manifested until later in life. To maintain the cervix in normal and comfortable position after subtotal hysterectomy in these cases is difficult, time consuming and unnecessary.

In cases of malignant lesions of the fundus and adnexa total abdominal hysterectomy is the operation of choice when the lesion is operable. It is nearly impossible to manipulate the uterus during hysterectomy without extruding some of the malignant cells into the cervical canal. It must be remembered also that 10 per cent of fundal malignant lesions have already extended to the adnexa and they must be removed also, regardless of the patient's age.

Carcinoma of the ovaries is best treated by total abdominal hysterectomy with bilateral salpingo-oophorectomy if the condition is operable. The rate of bilaterality of this disease is 50 per cent. The growth too often extends to the uterine cavity and potentially involves the cervix. However, occasionally subtotal hysterectomy is indicated if the total operation would be difficult and time consuming; then, radium and roentgen therapy is given to the cervical canal.

In cases of endometriosis and adenomyosis, the decision between panhysterectomy and subtotal hysterectomy should be made primarily on the basis of the condition of the cervix and also on the amount of fixation of the cervix by adenomatous tissue in the broad ligament attachments and in the rectovaginal tissues. When the patient is a young nonparous woman subtotal hysterectomy is indicated more frequently than panhysterectomy, especially if adenomatous lesions are located in the rectovaginal septum and rectal wall. The most satisfactory operation for menometrorrhagia with disseminated endometriosis is subtotal hysterectomy and preservation of some ovarian tissue if the cervix is good and if at least one ovary is free from the disease. When patients who have borne one or more children become sufficiently disabled by the disease to justify hysterectomy, panhysterectomy is indicated more frequently than subtotal hysterectomy.

The technic of panhysterectomy and of subtotal hysterectomy is described.

(The discussion of total vs. subtotal hysterectomy has been so thoroughly aired during recent years that it is difficult to present new angles of the question. Summarizing its present status, I believe it may fairly be stated that on the whole the total hysterectomists have won the field, in the sense that the great majority of gynecologists feel that the total operation should be done when its performance imposes no appreciable hazard to the patient. This of course means that the surgeon should be well qualified to do the operation, and that there should be no contraindication such as extreme obesity, serious systemic or constitutional disease on the one hand, or on the other hand some such local contraindication as an extremely deep pelvis or fixation of the cervix to the rectum, pelvic endometriosis or chronic pelvic inflammatory disease.

The condition of the cervix is often a determining factor in the surgeon's decision, and if it is the seat of marked chronic inflammatory disease he will be more inclined to do the total operation even though it is difficult than if the cervix is clean and healthy. On the other hand, even with an entirely normal looking cervix, many of us would prefer to remove it with the uterus when this can be easily done. As the author says, the cervix may seem quite normal looking on inspection and palpation and yet be the seat of a persistent chronic intracervical infection. Its retention under such conditions often means the persistence after operation of a troublesome leucorrhea, so that the patient is still left with a problem she may consider just as annoying as her original ailment. Nor is it rare for slight bleeding to occur, worrying the doctor as to the possibility of malignancy, and he will be likely to wish that he had taken the cervix out with the uterus. As a matter of fact, in the occasional case one feels impelled to enucleate the cervix vaginally in such cases.

Finally, cancer can develop later even in cervices which at the time of the hysterectomy appeared quite normal. When a surgeon encounters a case in which he chooses the supravaginal technique because of the technical difficulty and undesirable hazard which the total operation would entail, it goes without saying that the cervix should be carefully examined and such lesions as chronic cervicitis, erosions or polyps given proper treatment.—Ed.)

THE SELECTION OF PATIENTS AND A TECHNIC FOR VAGINAL HYSTERECTOMY

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In selecting the operation for patients which require hysterectomy of correction of prolapse it is well to remember that the vaginal route offers certain distinct advantages and that vaginal hysterectomy is decidedly the most adaptable and utilizable operation for prolapse.

At present the most common indication for vaginal hysterectomy is probably menorrhagia with anemia due to small fibroids or intrauterine polyps. Menorrhagia due to ovarian dysfunction with anemia which is not amenable to curettage and medical measures is another common indication. The author discusses the advantages of vaginal hysterectomy over curettage followed by the artificial production of the menopause by radium in such cases. Prolapse of varying degrees is another common indication for vaginal hysterectomy. Dysmenorrhea which requires hysterectomy for relief is a fairly common indication. Extensive chronic cervicitis occasionally is not amenable to conservative measures and even amputation in some cases will not completely eradicate the leucorrhea. Removal of the accompanying boggy subinvoluted type of uterus can be done vaginally with less risk than abdominally.

The author feels that generally vaginal hysterectomy should be reserved for uteri of such size that they can be delivered vaginally without morcellation. If morcellation is necessary for vaginal removal of a uterus there is more bleeding, more chance of infection and a remote possibility of cutting into and disseminating an unrecognized malignant lesion. In nulliparous and virgin patients usually a uterus 2 to 3 times normal in size can be delivered without morcellation or episiotomy. In multiparous patients with considerable relaxation a fair-sized fibroid uterus can readily be delivered.

If a malignant lesion is present in the body of the uterus, as a general rule abdominal panhysterectomy is preferable to vaginal hysterectomy. If an adnexal lesion of any size is present, as a rule it can be better disposed of abdominally. Previous pelvic operations may interfere at times with the execution of vaginal hysterectomy. In general it can be stated that all uteri are best removed vaginally if the organ can be delivered without morcellation and if there is no evidence of a malignant lesion or adnexal disease of a considerable degree.

The writer discusses the more common operations for the correction of uterine prolapse. He is satisfied that there is no single procedure for prolapse as adaptable or utilizable for all degrees of this disorder as vaginal hysterectomy. Most of the patients are well past the menopause and if there is to be any surgical procedure directed at the uterus it should be that of removal.

The technic described in this paper is quite similar to that used for total abdominal hysterectomy by Masson at the Clinic. It permits closure of the peritoneum under direct vision and support of the vaginal vault by the round, cardinal and uterosacral ligaments. A circular incision is made at the cervicovaginal juncture and a vaginal flap is dissected from the bladder. The bladder is then dissected from the uterus. An opening is made into the cul-de-sac and a clamp placed on the left uterosacral and cardinal ligaments. The uterine vessels are clamped and a ligature is tied on the uterosacral and cardinal ligaments. Next, the peritoneum is opened anteriorly. Ligatures are on the cardinal, uterosacral and uterine vessels on both sides. The fundus is delivered posteriorly, the round ligament, uterine end of the tube and utero-ovarian ligament are clamped, cut and ligated on either side. By gentle traction on the ends of all 8 ligatures the peritoneum is closed under direct vision, a running suture approximating the vesical reflection of peritoneum and the posterior reflection in the cul-de-sac. In this way all raw surfaces are placed extraperitoneally. An angle suture is then tied and approximated to the uterosacral and cardinal ligaments. The next most medial suture is placed through the vault and round ligament on each side. Then the round ligaments are tied together in the midline and the vault is closed over the stumps so that they lie between the peritoneum above and the closed vagina below.

(Next to the long drawn out discussion between the total and subtotal hysterectomists no question in the field of operative gynecology has been more widely discussed than that of the relative advantages and disadvantages of the vaginal as compared with the abdominal route for hysterectomy. The former of the two has been the preferred route in many clinics, and perhaps its chief champions have been the Chicago School of Gynecologists. That it has many advantages in a considerable proportion of cases I do not think permits of much doubt, and I feel that many of us, especially in the Eastern clinics, do not use it sufficiently often. The risk of subsequent vaginal enterocele, often stressed as a liability of vaginal hysterectomy, can be greatly minimized, though perhaps not entirely eliminated, by proper obliteration of the cul-de-sac at the time of operation.

On the other hand, I believe that the vaginal enthusiasts, and quite naturally, often succumb to the temptation of resorting to the vaginal method in cases in which the abdominal route would be safer and simpler. I have seen surgeons, especially in some of the European clinics, remove huge myomatous uteri per vaginam by morcellation. When watching such operations I could not help thinking how much easier the abdominal route would have been. Vaginal hysterectomy under such conditions is more of a surgical stunt that it is a wisely considered procedure for the individual case.

There are many other pros and cons, but the truth of the matter is that there is a very definite field for each of the two routes, and that while one naturally develops preferences for one or the other, every gynecologist should be equally well trained in both operations. He should adopt the operation to the individual patient rather than vice versa. In the paper abstracted above, Waugh gives a very sensible appraisal of the general problem, although it is quite evident that he belongs to the school in which the vaginal route is preferred to the abdominal in a large proportion of cases.—Ed.)

HYSTERECTOMY IN THE PRESENCE OF PERITONITIS, SALPINGITIS AND URETERAL OBSTRUCTION

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The warning by gynecologists against operating on patients in the presence of acute pelvic inflammatory disease is a wise one and usually should be heeded. However, there is an occasional patient for whom a pelvic operation may be lifesaving even with the very great risk of pelvic inflammation. Such an exception is reported by the authors.

A 31-year-old Negress was admitted to the hospital with pain in the suprapubic area and right lower abdominal quadrant of 6 days' duration. A large, hard, irregular and slightly tender mass extended from the symphysis to 4 cm. above the umbilicus. A vaginal examination showed the uterine corpus to be continuous with the abdominal mass. Laboratory study revealed a rapid sedimentation rate and leukocytosis. Acute rebound tenderness developed in the right lower quadrant 48 hours after admission and the temperature rose to 104 degrees F. Urologic consultation ruled out any morbid process in the urinary tract. Sulfadiazine and penicillin were administered. Seventy-two hours after the first episode, the patient complained of pain and appeared to be in shock. Glucose and whole blood were administered and, with the possibility of a ruptured appendix in mind, laparotomy was performed. Generalized peritonitis was found which had been caused by a ruptured right pyosalpinx. The uterus was greatly enlarged by multiple myomata. The abdomen was closed and penicillin was continued for 14 days, but the patient's condition remained poor. An exploration for a possible subdiaphragmatic abscess failed to reveal such a lesion. Sulfadiazine was again administered, but was discontinued when no clinical improvement was evidenced. Urological consultation now disclosed an acute suppurative nephritis on the right side, due to compression of the ureter by the enlarged uterus. A right ureterostomy was performed, but no appreciable improvement followed. Therefore, a supracervical hysterectomy and bilateral salpingo-oophorectomy were performed in spite of the patient's poor condition as well as technical operative difficulties. With transfusions of whole blood and the administration of penicillin and sulfadiazine, a gradual but excellent recovery was achieved. 2 figures.

(As the authors state, gynecologists agree as to the inadvisability of surgery in acute pelvic inflammatory disease. This viewpoint was general even before the advent of penicillin and sulfa therapy. I recall the widespread protest of gynecologists when, a good many years ago, a well-known general surgeon, the late R. C. Coffey, published an article in which he took exactly the opposite point of view.

While rupture of a pyosalpinx is relatively rare, it occasionally occurs, and in such cases operation is indicated. In spite of the peritonitis which is found in such cases, the patient's

general condition will often permit removal of the tube and not infrequently a more extensive operation, if the technical difficulties encountered are not great. In the case reported by Hall and Nelms, on the other hand, simple drainage, with penicillin therapy, was probably the wiser plan at the time, although the success of the more radical procedure carried out later when the patient's general condition was much worse, probably made them wish they had employed the radical plan at the first operation.—Ed.)

BLOOD PRESSURE AND GYNECOLOGICAL OPERATIONS

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Zentralbl. f. Gynäk, **69**: 381–396, 1947

In operative gynecology the surgeon sometimes fails to recognize the importance of high blood pressure as a factor in determining the success or failure of an operation, particularly if there is no diseased condition of the heart. This view is explained by the fact that blood pressure decreases after an operation.

The fault in this reasoning is that the decline is a passing symptom, while the disease of the vascular system remains.

In order to trace the effect of arterial hypertension on the whole circulatory system and to determine its reaction to operative interference 100 gynecological patients at the Women's Clinic of the University of Berlin were examined before and immediately after an operation and also during the postoperative period. Herzog's indirect method was used to measure the capillary pressure. Measurements were also taken of the arterial and venous pressure, supplemented by microscopic examinations of the capillaries in the fingernail grooves, which proved most valuable in differentiating hematogenic from nonhematogenic blood pressure. In view of the advanced age of most of the patients, fluctuations of 100–150 mm. Hg. in systolic, 50–100 mm. Hg. in diastolic, 30–100 mm. Hg. in venous pressure and 50–80 mm. Hg. in capillary pressure were regarded as normal.

A normal arterial blood pressure was found in 57 women, but the venous pressure remained within normal bounds in only 30, of whom 8 had an abnormally low venous pressure both before and after the operation. In 20 cases the venous pressure sank immediately after the operation, but rose to the original count during convalescence. The capillary pressure in all cases was parallel with the arterial pressure.

A rise in venous pressure above the normal rate of fluctuation occurred in the remaining cases. In some instances there was a pressure rise in the venous system with falling capillary pressure and irregular capillary circulation, producing incipient cardiac decompensation, which disappeared as the venous pressure declined again during convalescence. A cardiac insufficiency was discovered

in others. One patient died from myoma brought on by an obstruction. Among the women suffering from primary venous high pressure were many in whom an extensive varicosis was present. During convalescence one patient suffered from hemorrhages, two from septic infections, one from thrombosis and one from an embolism.

In the 43 remaining cases, 39 showed arterial hypertension, while in 4 there was hypotension. In 27 patients with "red" high blood pressure, 12 showed normal fluctuations of venous pressure and in 6 cases it was static. The other patients displayed marked fluctuations causing postoperative disturbances in the circulatory system. There were 2 fatal embolisms, 1 thrombosis, 1 case of peritonitis, 1 case of pneumonia, 1 of myocarditis, 1 of vitium cordis, and 1 of heart failure. Six women had an extensive varicosis.

The patients with so-called "pallid" hypertension displayed similar reactions. In 6 cases the venous pressure showed a normal postoperative rise and fall. Two patients developed a muscular heart weakness and 1 an embolism. Capillary action was disturbed in 2 cases. In the 6 remaining cases there were abnormal venous pressure curves. One patient developed thrombosis followed by an embolism.

The practical clinical conclusions to be drawn from the above analysis are:

1. That an abnormal rise in venous pressure accompanied by high arterial pressure may result in postoperative complications such as thromboses and embolisms.

2. Insufficient heart action characterized by a blue-gray coloring of the skin may be produced by this rise, in which case medical treatment must be used to overcome this deficiency.

3. Infections, hemorrhages and obstructions following an operation often lead to marked changes in the circulatory system, producing a marked decline in the flow in the blood vessels and stasis and coagulation in the capillaries.

4. A primary venous hypertension, which clinically is often combined with adiposis and wide-spread varicosis is also conducive to the development of thromboses and embolisms.

STERILITY

THE DIAGNOSIS AND MANAGEMENT OF STERILITY IN THE FEMALE

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The authors suggest a routine system of management for cases of sterility. It is estimated that 13 to 17 per cent of all marriages in this country are barren, and that 30 per cent of these are primarily the fault of the male. No analysis of a sterility problem is complete without thorough investigation of both partners. As a working definition one can assume that a state of sterility exists after at least one year of normal marital relations without contraceptive measures

The first step in the investigation of a sterility case is a general history to obtain information about the possibility of any existing systemic disease. The next step should be a careful and thorough gynecologic history, including a consideration of important items in the history of the husband as well. Next, the menstrual history is of obvious importance in relation to local pelvic disease and to constitutional and endocrine dysfunctions. The marital record requires careful investigation. At this point it is essential that both the husband and wife should have been separately interviewed before proceeding with further investigations.

The next step is a general physical examination of both husband and wife which can be of a simple routine nature; however, there may be reason for more special investigations later. In a careful gynecologic examination one should precede the pelvic examination with careful scrutiny of the breasts and abdomen, paying particular attention to the character and amount of mammary tissue and the amount and distribution of adipose tissue and hair. The pelvic examination must include bimanual palpation and inspection. The purpose of this examination is to determine the presence of any developmental defect, to unearth the presence of any pelvic infection and to search for the presence of any pelvic tumors.

For the purpose of special studies, the authors have these patients admitted to the hospital for a period of 24 hours. The first step is a complete blood count and urinalysis. A Wassermann examination of the blood is most important. The basal metabolism determination in the writers' hands has been the greatest single aid in evaluating these cases. They are inclined to disagree that a rate between minus 10 per cent and plus 10 per cent is normal; they consider a rate of minus 10 per cent as subnormal, and place the minimum normal rate closer to zero. The treatment for the hypometabolic group should be desiccated thyroid extract gr. $\frac{1}{2}$ b.i.d. to gr. 1 t.i.d.

The Huhner test should be included whenever possible in the special studies. The finding of living sperm in the vaginal pool is far less significant than its demonstration in the cervical canal.

Finally, the tubal patency test correlated with endometrial biopsy should be undertaken to complete the study. A single demonstration of non-patency is inconclusive and the test should be repeated at least 3 times. At the conclusion of insufflation, several specimens of endometrium are obtained for microscopic examination. The biopsy may yield information as to the quantitative effects of the 2 ovarian hormones upon the endometrium, and information as to whether ovulation occurred in a particular cycle. If ovulation has not occurred one is justified in instituting treatment with follicle-stimulating hormones with the hope of inducing ovulation. In many cases this form of therapy is combined with the use of estrogens, especially when the uterus is small and underdeveloped.

If cases are properly treated as outlined in this paper, conception will result in 20 to 25 per cent of cases. In addition, the less fortunate 75 to 80 per cent will have the satisfaction of thorough analysis, which will do much to relieve frustration, and perhaps may be encouraged to find happiness by adopting children.

(While this paper presents nothing especially new, it does describe a sensible plan of studying female sterility, without the probably unnecessary over-elaboration typified in some of the plans which have been published. The step-by-step method has always seemed to me to be the sensible one for most cases, without necessarily "shooting the works" in a single elaborate evaluation, although there is just as much room for individualization in the management of sterility as in all other clinical problems.—Ed.)

ARTIFICIAL INSEMINATION

E. CHESSER

London, W. 1.

Brit. M. J., 1: 738–739, 1947

The writer stresses the psychological factors involved in artificial insemination, which have received a minimum of attention as compared with the technical problems involved. It is by no means easy for even an expert psychologist to predict with confidence that any couple will not eventually experience strong emotional reactions which may increase in intensity as the years pass. However eagerly she may have resorted to the method in her desire for a child, the woman sooner or later is likely to experience a vague feeling of dissatisfaction with herself. She is almost sure to indulge in morbid musings about the unknown father of her child and may tend to grow away from the husband. The husband, whose self-esteem was dealt a blow by the mere revelation of his sterility, cannot help but consider the child a constant reminder of his inferiority and may come to hate it. The child will be the most pitiful victim of these and other consequences.

In the past, the writer had administered both types of artificial insemination,

but as a result of experience and reflection, would now take no case except with the husband as donor. The writer thinks it essential that all doctors, whatever their views, should present the psychological objections to their patients in the strongest terms.

(The author stresses a number of the psychological factors involved in artificial insemination which I do not believe have always been fully considered by the advocates of the method. From the standpoint of the husband's psychology, adoption would seem preferable to insemination, since the child in the latter case might well become, as Chesser states, a continuing reminder to the husband of his own inadequacy. The other factor mentioned by the author, that of possible constant morbid wonder as to who the real father of her baby is, would also appear to be not unimportant. For further comment, see the following abstract of paper by Jackson.—Ed.)

ARTIFICIAL INSEMINATION

MARGARET H. JACKSON

Crediton, Devon

Brit. M. J., **1**: 945, 1947

This writer states that it is of prime importance that doctors should think about and weigh the various aspects of artificial insemination in the light of their specialized knowledge and experience, setting aside in so far as they can, or at any rate recognizing, their own particular emotional bias in the matter. She refers to the letters of Dr. E. Chesser (May 24, p. 738) and Dr. F. Murray (June 7, p. 826) as cases in point of the emotional (as opposed to intellectual) judgments called forth by artificial insemination.

The only donors the present writer has ever met are unselfish and intelligent men who agree to give their spermatozoa, as they would blood for transfusion, to those in need. Further, the marriage is in danger of being wrecked by the resentment of a maternally inclined woman against her sterile mate, and the profound sense of failure and regret which must be felt by any but the most insensitive husband; this, in the author's experience is the situation to be solved. It lies within the doctor's sphere to try honestly and without prejudice or emotional bias to help such couples who consult him to find their particular solution. Finally, this writer suggests that it is too early in these days to pass sweeping judgments in either direction.

(Many gynecologists will question Jackson's belief that the donors in artificial insemination are always, or usually, influenced by purely idealistic and philanthropic considerations rather than by the fees which they receive for their specimens. Introducing another psychological factor to those discussed by Chesser in the preceding abstract, I suspect that there are many men who would not like the idea of having perhaps numerous unknown children of their own scattered among the families of their own or other communities, and

one would be inclined to think that those who have no objection to this are not likely to be highly idealistic from other points of view.

While Jackson appears to disparage such emotional and psychological objections and to stress chiefly the coldly intellectual angles, I do not think they can be thus lightly brushed aside. Together with the legal and theological connotations of artificial insemination, they serve to indicate that artificial insemination is not the simple glamorous affair which many sterile couples seem to consider it. They also explain why many, probably the majority of gynecologists and obstetricians, while freely conceding that the method is not infrequently successful in producing babies, feel that it is a rather disagreeable, somewhat subterranean form of practice which they prefer to leave to the few enthusiasts who are quite likely to be found in any large community. Incidentally, a comprehensive review of this whole subject has just appeared as these lines are written. (Abel, S. The present status of artificial insemination. International Abst. of Surg., in Surg. Gyn. & Obst., 85:521 (Dec.), 1947). This article will be commented upon in an early issue of the Survey.—Ed.)

MISCELLANEOUS

THE INCIDENCE OF PSYCHOSOMATIC DISEASE FROM A PRIVATE REFERRED GYNECOLOGIC PRACTICE

F. R. Lock and J. F. Donnelly

Bowman Gray School of Medicine of Wake Forest College, and North Carolina Baptist Hospital, Winston-Salem, N. C.

The authors state that the diagnosis of psychosomatic disease rests upon 2 points: 1. The absence of any demonstrable organic pathology or a lesion sufficient to cause the patient's complaints. 2. The presence of a definite emotional problem grave enough to justify such a diagnosis. The absence of a demonstrable pathologic lesion does not necessarily rule out a serious or fatal organic lesion which may not be detected by our present diagnostic methods. Each of the above criteria *must* be present for a diagnosis of psychosomatic disease.

The practitioner must keep in mind that both functional and organic problems occur in every practice, and must analyze each patient carefully from these points of view. Also it should be remembered that organic illness may give rise to fears which exaggerate the symptoms of the patient.

The purpose of the present paper is to call attention to the problem of psychosomatic disease and to evaluate the frequency of its occurrence. Many of the writers' patients had failed to respond elsewhere to adequate treatment of a pathologic lesion because an unsolved psychologic problem was present.

The total number of patients subjected to study was 1,759. The ages ranged from 8 months to 82 years. All patients were referred and of the white race. Three major groups were recognized.

Group 1 consists of those patients who had organic pathology to account fully for their symptoms. A total of 1,191 patients (67.6 per cent) had clear-cut pathologic problems. Group 2 included 220 patients (12.6 per cent) whose complaints could not be clearly justified by the existing pathology. Many of these patients improved strikingly shortly after the exact character of their illness was explained to them.

Group 3 contained 348 patients (19.8 per cent) who had symptoms in the absence of explanatory demonstrable pathology and, in addition, had emotional conflicts of sufficient severity to explain the complaints. These patients were divided somewhat arbitrarily into 9 subgroups, as follows: psychosis, 16; psychoneurosis, 130; simple adult maladjustment, 82; dyspareunia, 12; phobias, 59; frigidity, 32; pruritus vulvae, 10; hyperemesis gravidarum, 5; and miscellaneous, 7.

Case reports illustrative of groups 2 and 3 are presented.

The patients were analyzed statistically from 4 viewpoints, the first of which

was distribution according to age. No significant factors were noted except the expected preponderance of patients in the active sexual life (20 to 50 years). Secondly, the occupational distribution of the patients was studied; there is no conclusive evidence that occupation has any relationship to psychosomatic disease. Thirdly, previous operations were noted. There was a definite tendency toward an increased number of previous operations in groups 2 and 3. Lastly, the ultimate disposition of the patient was noted. Seventy-six per cent of the patients were handled medically, 21.7 per cent surgically, and 2.3 per cent psychiatrically. The only psychiatric referrals were in group 3 where, out of 348 patients, only 25 would accept psychiatric care.

The incidence of psychosomatic disease in this referred gynecologic practice was approximately 33 per cent. While this figure is not as high as in some other specialties, it is still sufficient to demand attention.

(This is an interesting and worthwhile study of the psychosomatic factor in gynecological patients. Everybody accepts its importance, but the statistical studies of the authors, although they cannot aim at sharp precision in the grouping of their patients, must impress one with the great numerical frequency with which the psychosomatic factor obtrudes itself into the clinical picture of patients who actually have pelvic pathology, as well as the frequency of syndromes often receiving gynecological treatment, unfortunately sometimes surgical, when there is no local pathology and it is the psyche which needs treatment.

It is of interest to note that only a very small group were referred for psychiatric treatment, and this may be interpreted as a compliment to the gynecologists handling the cases, indicating that they were probably pretty good amateur psychiatrists themselves, as all gynecologists should be. The treatment of such cases is often time consuming and calls for much patience, necessitating reassurance, simple instructional explanations, and a real interest in the particular patient's personal and domestic problems. Good results are not to be expected from hurried and perfunctory examinations by busy practitioners tensely anxious to get on to the next patient.—Ed.)

THE PSYCHIC COMPONENT OF PAIN IN GYNECOLOGY AND OBSTETRICS; A SENSORY CONDITIONING PROCESS

W. E. Hunter

Los Angeles, Calif.

Am. J. Obst. & Gynec., 54: 848–854, 1947

The author attempts to show that the ever-increasing afflictions of humanity are for the most part disorders of sensory perception and not symptoms of structural pathology.

The perception of pain is a psychobiological product of evolution and its intensity is the result of a sensory conditioning process. The psychic factors in gynecologic and obstetric disorders develop for the most part through exaggeration of normal physiologic impulses. By suggestion, persuasion, introspection

and fear, some patients perceive subliminal impulses of which they would normally be unaware.

In all therapies, the attitude of the patient is a most important factor. This is particularly true in either ameliorating or intensifying the discomforts of pregnancy and the pain of parturition. It is equally true of pelvic pain, particularly essential dysmenorrhea.

It is important that the practicing physician recognize pain as a perception and not judge it solely by the reactions. Medicine of the future must be more educational than curative and attack environmental causes of disorders rather than structural changes of disease if it hopes to overtake the rate of increase of ailments.

NOTICE

The American Gynecological Society will hold its next annual meeting on May 24, 25 and 26 at the Williamsburg Inn, Williamsburg, Virginia, under the presidency of Dr. Emil Novak, Baltimore, Maryland.

AUTHOR INDEX
APRIL, 1948

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Obstetrics

PELVIC MENSURATION:

A STUDY IN THE PERPETUATION OF ERROR*

NICHOLSON J. EASTMAN

From The Department of Obstetrics, Johns Hopkins University and Hospital

Contraction of the pelvis with consequent disproportion between the size of the infant and that of the bony birth canal, is such a simple concept that one might suppose it attracted attention in the earliest times as a cause of dystocia. Actually, it was not until the 18th century that the veriest idea of correlating difficult labor with pelvic deformity became extant,—long after more abstruse conditions such as extrauterine pregnancy and placenta previa were widely recognized. Although the principles of clinical measurement of the pelvis were established by William Smellie in 1754, the subsequent introduction by other practitioners of certain fallacious assumptions postponed any correct acquaintance with that discipline for a hundred years and, even after that, many of the more deeply rooted errors continued to persist. The evidence seems clear, indeed, that there is no phase of obstetrics which has been so fraught with blunder, oversight and floundering as has pelvic mensuration; and in view of the present status of the subject—diverse notions as to what constitutes disproportion, conflicting opinions about the value of x-ray mensuration, and so forth—it would appear that this old legacy of error is still with us.

It is the purpose of this communication to sketch the history of error in pelvic mensuration from the earliest times to our own day, with the thought in mind that this background may prove helpful in evaluating present trends and in mapping future progress.

It seems inconceivable that two primitive ideas, both on first glance rather innocuous, should have forestalled for more than 1500 years any thought of dystocia due to contracted pelvis. Nevertheless, it is just to two such misconceptions that the belated appearance of pelvic contraction in the annals of obstetrics is due. One of these was the idea that the symphysis pubis separates in labor to allow the infant to pass through; the other was the belief that the baby gains egress from the mother's body by its own physical efforts, the uterus being merely a passive sack.

The doctrine that the pelvic bones separate in labor seems to have had its origin in one of the Hippocratic works, "The Nature of the Infant," where the following statement is found: "Among women in labor, those who suffer most are the primiparae because they have not previously experienced this kind of suffering.

* The Charles Sumner Bacon Lecture for 1947–48, delivered at the University of Illinois, Chicago, Illinois, April 14, 1948.

They suffer in the whole body, but especially in the lumbar region and ischia; for their ischia separate."[1]   Although a few scholars have quibbled about the meaning of the term "ischia" in this passage, Fasbender,[2] the most eminent historian of obstetrics, is certain that it refers to the bony pelvis and most other authorities concur.   In any event, subsequent writers in antiquity leave no doubt that separation of the symphysis in primiparae was universally regarded throughout that era as essential to normal labor.   Thus, Soranus of Ephesus, who quoted or paraphrased most contemporary authors in addition to giving his own opinions, summarized belief in the 2nd century A. D. as follows: "Difficulties (in labor) may also originate in the body . . . because the pubic bones have grown together, so that they are not capable of separating in parturition, for in women the pubic bones do not fuse into a solid joint as in men, but are bound to each other by a strong ligament."[3]   That this doctrine prevailed throughout medieval times and even to the beginning of the 18th century is indicated by the following passage from Deventer's Novum Lumen, published in 1701: "The consistency of the bones is not the same in all subjects.   In some a good deal of cartilage is present; in others ossification has taken place to such an extent that the pelvis seems to be one bone.   This explains why some women are delivered with less pain than others; and one feels in advance that the hardness of these bones prevents them from giving way to the effort which the fetus makes to get out.   These bones are articulated by a little cartilage or by a ligament capable of extension or relaxation provided it is not ossified.   This confirms the opinion of those who attest that they have felt a separation of the os pubis in very difficult labors.   It is necessary to agree, however, that the case is rare and that this separation is of little help."[4] As the last sentence of this quotation implies, Deventer, in 1701, was one of the first to attempt to refute this age-old teaching.

The above concept, namely that the pelvis is an elastic ring, capable of enlarging as necessary to permit passage of the infant, would naturally nullify at once any thought that narrowness of the bony passages per se could impede the birth of the infant.   In other words, any case of difficult labor which in modern times would be attributed to contracted pelvis, was ordinarily explained before 1700 on the grounds that the ligaments of the pelvis failed to stretch.   With this idea of the mechanism of labor in mind, there could be no such thing as dystocia due to contracted pelvis, as we understand the term; and pelvic mensuration would have been, of course, quite meaningless.   It would have been, indeed, about as significant as measuring the lumen of the nonpregnant cervix in order to ascertain if a full term infant could pass through it.

The other ancient concept which forestalled recognition of pelvic contraction is to be found in the same Hippocratic work, "The Nature of the Infant," and reads in part as follows: "When the time for parturition arrives, the infant, moving itself and agitating its feet and hands, ruptures the interior membrane and thereupon the other membrane, which is weaker, ruptures also. . . . The membranes being ruptured, the infant is loosed of its fetters and makes its way to the outside by agitating itself.   While advancing the infant forces and dilates the womb in its passage. . . . If the nourishment coming from the mother to the infant is faulty, this is a cause of premature birth."[5]   In sum, the Hippocratic

school believed that the 'mechanism ·of labor depended solely on the muscular activity of the infant who, as term approached, experienced need for additional food and so ruptured the membranes, dilated the birth passages and pushed itself out. The pains of labor were attributed to the dilatation and stretching of the birth passages. This general concept was universally held until well into the 18th century. Thus, in the above quotation from Deventer (1701), it will be noted that he uses the phrase "the effort which the fetus makes to get out."

If the phenomenon of labor depended solely on fetal activity, it would follow as a necessary corollary that fetal death would bring labor to a standstill. Now, in the presence of pelvic contraction, it is common knowledge that fetal death is very likely to ensue after a day or so of labor because of compression of the cerebral structures; and, until modern times, it was only after such a period of time that male physicians were called by midwives to see such cases. Hence, the picture which obstetricians generally held of prolonged, futile labor was one in which the infant had already succumbed. It was only natural, therefore, to incriminate fetal exitus as the cause, for, in view of the above teaching, there was no need to seek for further explanation.

Had it not been for a gross oversight, these two old errors might have been ferreted out of obstetrics more than a hundred years earlier than they were; but, somehow, obstetricians paid no heed to the searching studies of Vesalius and his pupil, Arantius, on the pelvis, published in 1572. Not only did the observations of these Italian anatomists discountenance the ancient doctrine of pubic separation, but they provided the first valid statement in history on the anatomy of the pelvis, both normal and contracted.

Vesalius' condemnation of the old hypothesis of symphyseal separation is unequivocal and reads in part as follows: "The pubic bones are joined together by a cartilage. . . . This is identical in men and women. . . . In parturient women these bones do not become separated nor do they in the lower animals."[6] The entire Vesalian school was in complete agreement on this point and, indeed, one member of it, Realdo Colombo, commented that the pubic bones are so stoutly joined together that it is difficult to separate them, even with a knife; and he termed the whole ancient concept "ridiculous."[7]

The most extensive statement from the Vesalian school on the pelvis came from Julius Caesar Arantius, who not only reiterated the foregoing viewpoint but contributed many sound observations on pelvic contraction, both anatomic and clinical. Since this represents the first recognition of, and the first valid pronouncement on, pelvic contraction in the history of obstetrics, (Figs. 1 and 2), it is quoted in full:

THE PRINCIPAL CAUSE OF DIFFICULT LABOR IS RELATED*

Ch. 39

"The divine Hippocrates, as well as others, has indeed very well described several causes of difficult labor which are seated in the woman. Nevertheless,

* Translated from the original Latin by Dr. Owsei Temkin, Associate Professor of the History of Medicine, Johns Hopkins University School of Medicine, to whom I am greatly indebted.

IVLII CAESARIS
ARANTII
BONONIENSIS
Medicinæ, atq; Anatomes Pub. profefloris,

DE HVMANO FOETV LIBER
Tertio editus, ac recognitus
EIVSDEM
ANATOMICARVM OBSERVATIONVM LIBER:
A C
DE TVMORIBVS SECVNDVM LOCOS AFFECTOS LIBER
Nunc Primum editi.

**Ad amplifsimum Cardinalem Henricum Caetanum
Bononiæ Legatum à Latere.**

CVM PRIVILEGIO.
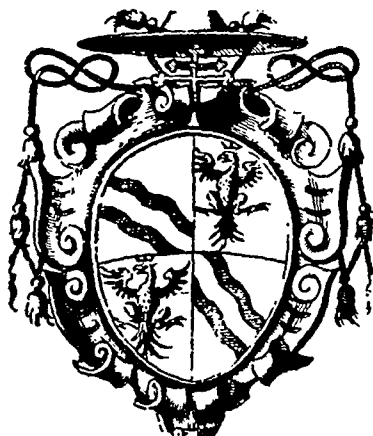
VENETIIS, Apud Iacobum Brechtanum, 1587.

FIG. 1. Title-page of the first book to discuss pelvic contraction; "De Humano Foetu Liber," by Julius Caesar Arantius. This title-page is that of the third edition (Venice, 1587) in which is incorporated another work of Arantius, the "Anatomicae Observationes." The first edition of "De Humano Foetu Liber" was published in 1572.

they have, in my opinion, veiled the principal cause in silence. For, since I have been wont for so many years, frequently, and with God's mighty assistance, to help women in difficult labor, I have been in a position to explore that cause sufficiently: Indeed, the most important point lies in the conformation of the

ANATOMICAE OBSERVAT. 105

Difficilis partus præcipua caufa redditur.
Cap. X X X I X.

Arturiendi difficultatis,plures caufas, ex parte mulieris,optimè quidé;tùm Diui-nus Hippocrates,tùm cæteri fcripferût: Omniũ tamen,mea fententia,præcipuam,filentio inuoluerunt. Nam , cùm ipfe,iam tot annos,ęgrè parturientibus, fæpenumerò, Deo benè iuuantè, opem afferre ꞇ ꞇnfueuerim, ea mihi fatis explo-rata effe potuit;etenim rerum fumma,in ipforum ofsium pubis , prima illa, quæ in vtero fit, con-formatione , refpofita eft:nam,fi offa,prout con-uenit, probè fuerint conformata, non admòdum lata,extrorfumque conuexa, quod fubijcitur con cauum, conuexo , proportione refpondet,femi-circularifque cauitas ,arcus in modum eminens, fub pubc latet, fimulque inter pubem,& coccy-gem, idoneum fpaciùm relinquitur quod prodi-turo foetui , facilem præbet aditum , & quamuis interdum, uel duplicatus puer effet, uel malè po-fitus, manum, aut pedem produceret , opem fe-renti , ad eum dirigendum,fapientis artificis ma-nui , nulla fefe offeret difficultas. Sin autèm pubis offa, formatricis facultatis uitio; parum aptè difpofita fuerint, quod.f.iufto fint latiora, exteriorique regione itacomprefla, ut potius in-

O trò

pubic bones themselves as they are first formed in the uterus. For if the bones have been well and properly formed, not too broad, convex on the outside, and if

the concave part which is placed under the convex corresponds proportionally, if a semi-circular cavity and a lofty arc are concealed under the pubic bone, if at the same time favorable space is left between the pubic bone and the coccyx, which will allow an easy entrance to the advancing foetus—then, even if, as sometimes happens, the child be doubled up or have a bad position, presenting with a hand or foot, no difficulty will offer itself to the helpfully directing hand of the wise master.   If, however, the pubic bones, due to the fault of the formative faculty, have not been favorably arranged, that is to say if they are too broad and in the exterior region so compressed that they become humped rather than concave on the inside, and if they come very near the sacrum and coccyx, then the parts of the parturient become so narrow that the road is not wide enough for the foetus, even if turned upon its head according to nature, especially if it is endowed with a relatively large and solid head.   The reason is that the foetus, with its occiput or sinciput gets so stuck to the posterior part of the pubic bone that it can by no means proceed on its own account.   And, what is worse, the helping hand of the operator which is about to bring aid, can not reach there because of the narrowness of the parts.   Thus it usually happens that not only the foetus but the puerpera herself succumbs; sometimes also necessity herself compels the extraction of the child, which is already dead and putrescent, with difficulty and piece by piece.

"But when matters have become so difficult and have reached the point that grave danger threatens and that we remain in doubt about the child, whether it might live or die—what then should a Christian physician do and what resolution should he form?   For if he leaves the patient without help, he will acquire the reputation of being inhuman.   If, on the other hand, he rashly employs the hand and dismembering instruments and kills the foetus which perchance is still alive, and has not yet been abluted from the sacred font, so that the woman be saved, he will burden his own conscience since evil should never be done that good may result.   And he will have to render an account of his stewardship to the Highest, all the more so since the secrets of God's supreme wisdom escape us and since it usually happens that, due to the very great difficulty of the work and its long duration, the strength of the mother gives out during the operation and malicious accusation of the art arises.   For the reasons stated, when spurred on by Christian piety but with misgivings in my mind I happen to visit a woman in difficult labor, I first of all usually inquire from the midwife present whether the pubic bones of the confined woman are relatively prominent or compressed, whether the parts are accessible to the hand and which is the infant's position.   Then, stepping nearer, I explore the woman's strength and vital force and, if they are in excellent condition, I lay my hand to the parts and acquaint myself better with every detail.   If now the narrowness of the bones has not caused the delay and if I find an easy access, having implored the help of Almighty God, I accede cheerfully to the task and, for the most part, bring it to a happy conclusion.   If, however, the female parts, because of a relatively compressed pubic bone show rable narrowness, I deem it better to take to an honorable flight and to from the task, than to take such grave hazards upon myself, the more

so if the woman's constitution has been weak. Yet this by the way as a friendly warning to the younger men so that they may disregard any persuasion and in such a grave affair may never do anything rashly, imprudently or negligently, keeping the last judgment in mind. But with all this I shall have to deal at greater length and ex professo in the Commentary on Women's Diseases by the Divine Hippocrates."[8]

The refractoriness of physicians of the time to the conclusions of Arantius is difficult to understand; but, as indicated above, his views are not even mentioned in the writings of the following century and pelvic contraction continued to be ignored. For instance, in the textbook of the most eminent of 17th century obstetricians, Francois Mauriceau, published in 1668, pelvic contraction is dismissed with the brief sentence: "Crooked persons (hunch-backed) have sometimes the bones of the pelvis not well formed."[9] In the whole work there is no other mention of pelvic contraction, despite the fact that he lists innumerable other causes of difficult labor. Moreover, in a subsequent work of Mauriceau, published in 1695, reporting observations on 700 complicated obstetrical cases (in the course of 3000 seen in 25 years), there are only two examples of pelvic contraction.[10] One of these was the famous case in which Hugh Chamberlen tried futilely to effect delivery by forceps in a rachitic dwarf with extreme pelvic deformity, but failed and the patient died 24 hours later. Postmortem, Mauriceau demonstrated a rupture of the uterus, but was so little impressed by the pelvic contraction that he made no further mention of it.

The credit for founding our knowledge of pelvic contraction is generally given to Hendrik Deventer, a Dutchman who, after following the trade of a locksmith in youth and later the profession of orthopedics, turned to obstetrics and brought to it the mechanical attitude of mind which those two vocations imply (Fig. 3). In his celebrated "Novum Lumen,"[11] published in 1701, there appears (except for Arantius) the first accurate description of the pelvis and the first emphasis on contraction of the pelvis as a cause of dystocia. As noted previously, he opposed the hypothesis that pubic separation played an important part in labor. His detailed knowledge of the pelvis made it possible for him to classify several architectural types, such as the pelvis nimis parva (generally contracted) and the pelvis plana (inlet only contracted). His statements on the clinical course of labor in pelvic contraction are far in advance of his time and bespeak extensive clinical experience. Thus, he writes of the extreme lengthening of the head which occurs in labor with the generally contracted pelvis, the resultant congestion of the head and the likelihood of fatal injury therefrom. In flat pelves he warned against too rapid and forceful passage of the head through the pelvis lest the infant suffer grave damage. In addition, he described fairly accurately the axis of the birth canal. His works were widely studied, carried great influence and, not without reason, has he been called the "father of modern midwifery."

Although Deventer's emphasis on pelvic contraction as a common cause of dystocia deserves lasting remembrance, his conception of the specific type of bony deformity most often concerned, was quite erroneous. It was based on his belief

that in normal labor the sacrum and/or the coccyx swings backward to make way for the child. Thus, he writes: "The increase in the size of the pelvis at the time of parturition results from the fact that the os sacrum swings backward,—or, at least the tip of it which we call the coccyx. And that which makes labors very

FIG. 3. HENDRIK A. DEVENTER (1651–1724)

laborious is due less to the small diameter of the superior strait of the pelvis than to the scantiness of the space between the ischial tuberosities and the coccyx."[11] Later on, he recommends that the whole hand be introduced into the vagina in order to push back forcibly the obstructing sacrum and coccyx. In keeping with this viewpoint the illustrations in his book tend to exaggerate the smallness of the space between the coccyx and the ischial tuberosities, as shown in Fig. 4.

It was a small-town practitioner of Vallognes, France, Guillaume Mauquest de la Motte, who first enunciated the fact that diminution in the size of the inlet is the most common type of pelvic contraction and is a frequent cause of prolonged and difficult labor.   After finishing a 5-year course of training in the Hotel Dieu
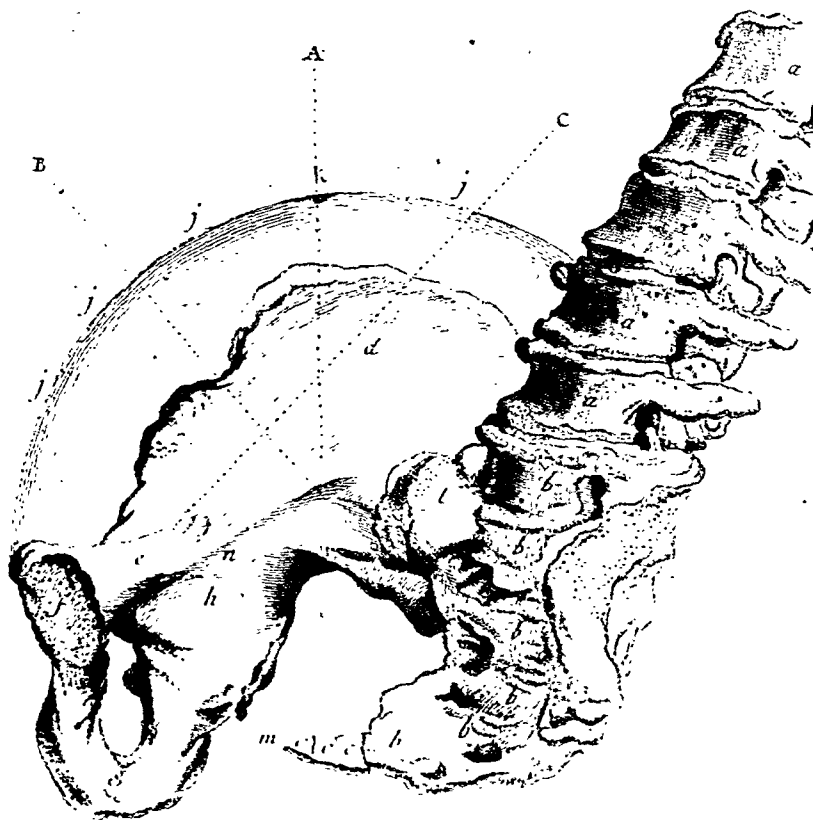
Fig. 4. The pelvis as pictured by Deventer in his "Novum Lumen," published in 1701. It illustrates his concept that proximity of the lower part of the sacrum or coccyx to the pubis represents the most common type of pelvic contraction.

in Paris, de la Motte established practice in his home town and after 30 years of obstetrical experience, published in 1722 his "Traité Complet des Accouchements."   This is not a systematic textbook, but rather a seriatim account of a lifetime of observation and reflection on things obstetrical.   In Book 2, Chapter 5, he states: "The most important cause of long and difficult labor is when the lower lumbar vertebrae, together with the superior part of the os sacrum, or even this

bone alone, is advanced too far within, or when the superior part of the pubis is flattened,—in such a manner as to allow but a very small space between the symphysis pubis and sacrum. . . . It is this space—whether it is more or less large—which renders the passage of the infant more or less easy."[12]   He rightly stated that the coccyx plays no role in impeding labor.   The newness of this whole idea is indicated by the fact that de la Motte questioned whether it would be accepted, writing: "These innovations may not be to the liking of certain accoucheurs; but, as Amerigo Vespucci discovered a quarter of the world only by dint of navigation, and as Harvey discovered the circulation of the blood only by dint of prolonged anatomical work, so I would not advance such a proposition, dealing with the greatest difficulty of labor, had I not been persuaded by an infinite number of experiences."[12]

By the first quarter of the 18th century, then, the concept of pelvic contraction had at last been grasped and its most common site assigned to the superior strait. As yet, however, no mention of pelvic mensuration is to be found.   This discipline was of dual origin.   It came in part from the theorizing of an ingenious and geometrically minded French accoucheur, André Levret, and in 'part from the judicious clinical observations of the greatest of British obstetricians, William Smellie.

No better idea of Levret's approach to obstetrics can be had than from the title of his textbook published in 1753: "The Art of Accouchement as Demonstrated by the Principles of Physics and Mechanics."[13]   Surely at that time there was need for such an approach, and Levret's preliminary comments on the pelvis are refreshing in their originality and correctness.   He was the first to describe the three pelvic planes, that of the inlet, the midpelvis and the outlet; moreover, in noting that the midpelvic plane is the largest of the three, he was astute enough to add "except for the space extending between the two ischial spines."   He aptly likens the shape of the inlet to that of the heart on a playing card.   He cites specific measurements for the various pelvic dimensions, observing that the posterior half of the outlet forms an equilateral triangle, its base being the distance between the ischial tuberosities and its apex the junction of the sacrum and coccyx.   In the normal pelvis he finds that any side of this triangle should measure about 10 cm.   He also gives dimensions for the transverse, anteriorposterior and oblique diameters of the superior strait, but states that the anteriorposterior is larger than the transverse, the former measuring between 12 and 15 cm. and the latter about 12 cm.   It is easy to criticize Levret on the grounds that this relationship is just the reverse of what actually obtains in the average pelvis, but the error would seem excusable on the basis that he may have chanced upon some anthropoid pelves.   All his measurements were made on fresh cadavers.

With such a background it might seem that Levret would have been just the man to elucidate the long neglected problem of pelvic contraction.   Unfortunately this was not to be the case; for despite his promising approach to the subject, he very shortly goes awry and before many more pages are past, it becomes clear that we are back once more in the familiar annals of fallacy.   The fact that Levret did not make further contributions to this field may be traced
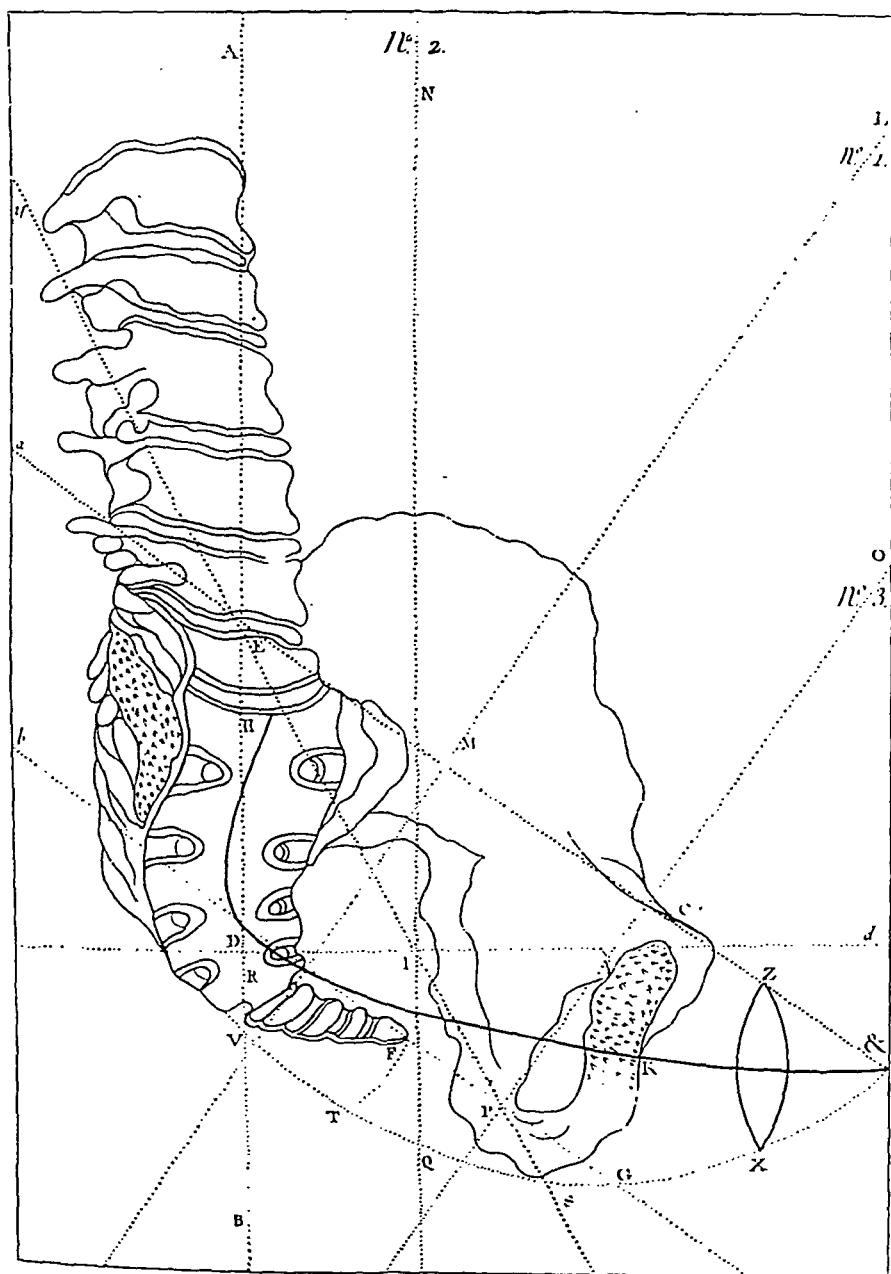
FIG. 5. The pelvis as analyzed by Levret, showing the various planes, diagonals and parabolas, etc., which he constructed upon it.   The whole geometrical concept which he wishes to illustrate here is based on the premise that, with the woman in the standing position, the line Dd is parallel to the horizon, an obvious error. From his "L'Art des Accouchemens demontré par des Principes de Physique et de Mecanique, etc."   Paris, 1753.

to two errors.   In the first place, he apparently had separate pigeon-holes in his mind for pelvic mensuration and for clinical obstetrics and never allowed one to have anything to do with the other.   For instance, he asks the question: how can the accoucheur ascertain whether pelvic contraction makes delivery per vaginam impossible?   We might expect from this painstaking student of dimensions, planes and triangles an answer couched in terms of precise measurements, but actually his reply dates back to Arantius: "when the accoucheur cannot push his fist through the pelvis."   This criterion of pelvic contraction was part and parcel of obstetric teaching at the time and any other obstetrician or midwife of that or the preceding century would probably have made the same answer.   In other words, to clinical mensuration Levret contributed nothing.   Levret's second lapse was his infatuation with intricate geometrical theorizing on the pelvis,—a pitfall which has ensnared not a few later obstetricians down to the present day of x-ray pelvimetry.   Fig. 5, reproduced from Levret's textbook, shows the elaborate system of planes, diagonals and parabolas which he managed to construct on the pelvis, all for the purpose of showing that the position which midwives had their patients assume was incorrect.   Aside from the fact that all the lines, points and curves shown are meaningless from a clinical viewpoint, his fundamental premise is erroneous, namely, that the inclination of the inlet in the standing position is 35°, rather than 55°, the correct figure.

But if Levret's contribution to clinical mensuration was negligible, he will always be remembered gratefully as the originator of the pelvic curve of the forceps, his greatest achievement.   But this sumptuous courtier himself (Fig. 6) would probably have esteemed another accomplishment of his life still higher. Wherever his name appears, be it on the title pages of his book or at the foot of his complicated diagrams, there is always seen the same invariable subscript; and, indeed, if Levret could have written his own epitaph, it would doubtless have been that same subscript: "Accoucheur to Madame La Dauphine."   Today, and in modern parlance, Levret would probably have been regarded as a rather "cockey fellow," (or, as Thoms remarks more elegantly, "a man of independence of character"),—as attested by the following story.   When Levret was called to attend the Dauphiness that lady remarked "You must be pleased, M. Levret, to deliver the Dauphiness.   That will make your reputation."   To which Levret is said to have replied "If my reputation were not already made, I should not be here."[14]

Quite a different person was William Smellie and quite different his contributions (Fig. 7).   It would be presumptuous to attempt to survey in the brief limits of this review Smellie's monumental additions to obstetrics; and it will suffice to say that not the least of his accomplishments was to have devised the diagonal conjugate measurement, the most important contribution which has ever been made to clinical pelvimetry.   In his "Collection of Cases and Observations in Midwifery," published in 1754, Case 4, in Collection 21, reads in part as follows: "In the year 1742, my attendance was bespoke to a woman who had been four times delivered by another gentleman of dead children; and it was alleged her pelvis was so narrow and ill-formed that she could not possibly bear a

live child. . . . I felt the head resting above the pubes, and was agreeably surprised to find the pelvis was not so narrow as it had been described; for, with the tip of my finger I could hardly reach the jetting forward of the last vertebra of the loins

FIG. 6. ANDRE LEVRET (1703–1780)

and upper part of the sacrum; from which circumstance, I understood the pelvis at that part was not above half, or three-quarters of an inch, narrower than those that are well formed. I therefore hoped that if the child was not large it might be saved. . . . The nurse had put her to bed, and I, during a strong pain, felt the

membranes pushing down large and full through the os externum. . . . I perceived the head was at the lower part of the pelvis. I had scarcely time to put on a nightgown when another pain returned, and the woman was immediately delivered of a small child."[15]   Under Number 3 of Collection 1, he writes as follows: "The most common distortion of the pelvis, is, from the protrusion or jetting

FIG. 7. WILLIAM SMELLIE (1697–1763)

forwards of the last vertebra of the loins, with the os sacrum, and sometimes of two or three of the lowest vertebral bones. I have been concerned in a few cases; and, in particular, was called to three women, in whom the pelvis was so narrow, that the distance between the lower vertebra and the pubis, did not exceed two inches and a half. The first I delivered four times, but found it impossible to save any of the children, except one, which was small, and even in that, the

shoulder was dislocated." In the following paragraph he notes: "I have been called to several others, where the pelvis appeared, at that part, not to exceed three inches, or three inches and a half. When the children were large, it was impossible to save them, either by the forceps or by turning; but when I was called in time, and found them small, or even of a middle size, the patient was commonly delivered by one of those methods, if the pains were not sufficient." (Fig. 8)
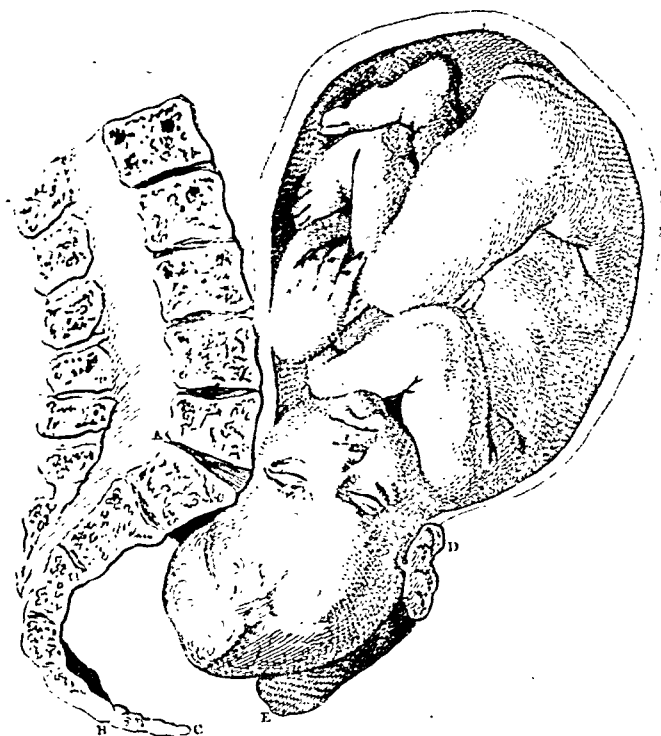
Fig. 8. Plate 27 in Smellie's "Anatomical Tables," London, 1787, showing that an extremely contracted pelvis will sometimes allow the passage of the infant provided it is small.

Even these two brief quotations are enough to attest the vast distance which separated Smellie from his predecessors. He not only introduced a practical and dependable method for measuring inlet contraction, but stressed the importance from a prognostic viewpoint of the relationship between pelvic contraction and the size of the infant. Had his diagonal conjugate measurement been adopted as a corner stone upon which to base further acquaintance with the clinical behavior of the contracted pelvis, the diagnosis and management of this complication, down to our own day, would have been sounder than it has been.

But again error crept in,—this time, in two ways; first, in the invention of a series of ultra-complicated instruments to measure the pelvis and second, in the development and spread of external pelvimetry as a substitute for internal mensuration.

In a fascinating little book by Felix Skutsch, published in 1887, he traced the history of pelvimeters from the latter part of the 18th century to his own times.[16] Therein are listed and illustrated some seventy instruments for pelvic mensuration which in their ingenuity, intricacy and impracticality, rival the drawings of our modern cartoonist, Rube Goldberg. Even a cursory glance at a few of these devices (Figs. 9–16) will arouse the greatest admiration not only for the inventive genius of their makers but also for the fortitude of the women who submitted to their use. Aside from their impracticality, these instruments reflect a trend which is worth noting in relation to certain modern tendencies in x-ray pelvimetry, namely, over-emphasis on the clinical import of certain minutiae of pelvic mensuration. These elaborate pelvimeters, along with the planes and parabolas of Levret, may be regarded as the forerunners of our more modern planes of Hodges and of some of our present-day indices which purport to predict whether or not vaginal delivery will be possible. As will be reaffirmed subsequently, the prognosis of labor in the presence of pelvic contraction does not lend itself so simply to the precepts of analytical geometry.

A much more serious error, because of its widespread acceptance for more than a century and a half, was the introduction of external pelvimetry by J. L. Baudelocque in 1775, especially the introduction of the external conjugate measurement, often called the Baudelocque diameter. In Baudelocque's opinion, this dimension was regularly about 7.5 cm. greater than the conjugata vera and hence, through simple subtraction, yielded the conjugata vera.[17] Of all the pelvic measurements which have been recommended, the Baudelocque has probably been more widely employed and, until very recently, more universally depended upon than any other index of pelvic contraction. The number of cesarean sections which have been performed solely because of a reduced Baudelocque diameter and, contrariwise, the number of women who have been allowed to suffer hours of hopelessly obstructed labor because this dimension was normal, are legion. An insidious feature of this measurement is that it does contain an element of validity because, in most cases, it does bear the approximate relationship to the conjugata vera which Baudelocque claimed; however, as shown in Fig. 17 the difference between this dimension and the conjugata vera may vary, even in a series of 115 cases, between 5 and 13 cm. (Dippel[18]). This means that it is not very unusual for a woman to have a Baudelocque diameter of 19 or 20 cm. with contracted internal measurements and, contrariwise, a measurement of 16 or 17 with a normal inlet. This criticism of the diagonal conjugate is not new since it was made by contemporaries of Baudelocque, was emphasized in the 19th century by Michaelis[19] and in the present era by Thoms.[20] However, as we have already seen, once error gets the upper hand in this field, it is hard to down.

As Thoms pointed out a decade ago, the intercristal and interspinous dimensions of the ilium are even of less clinical import. Some five years ago we had the
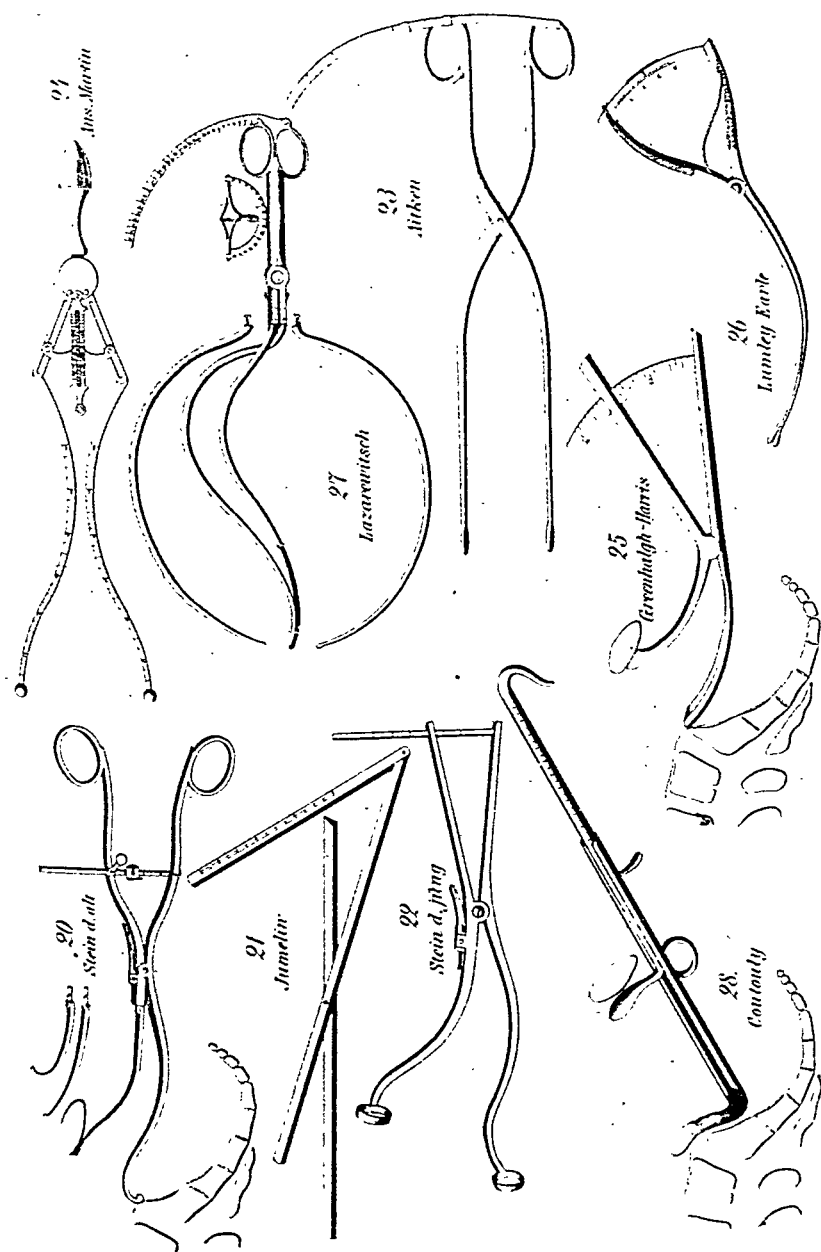
Fig. 9. Various Types of Pelvimeters as Illustrated by Skutsch
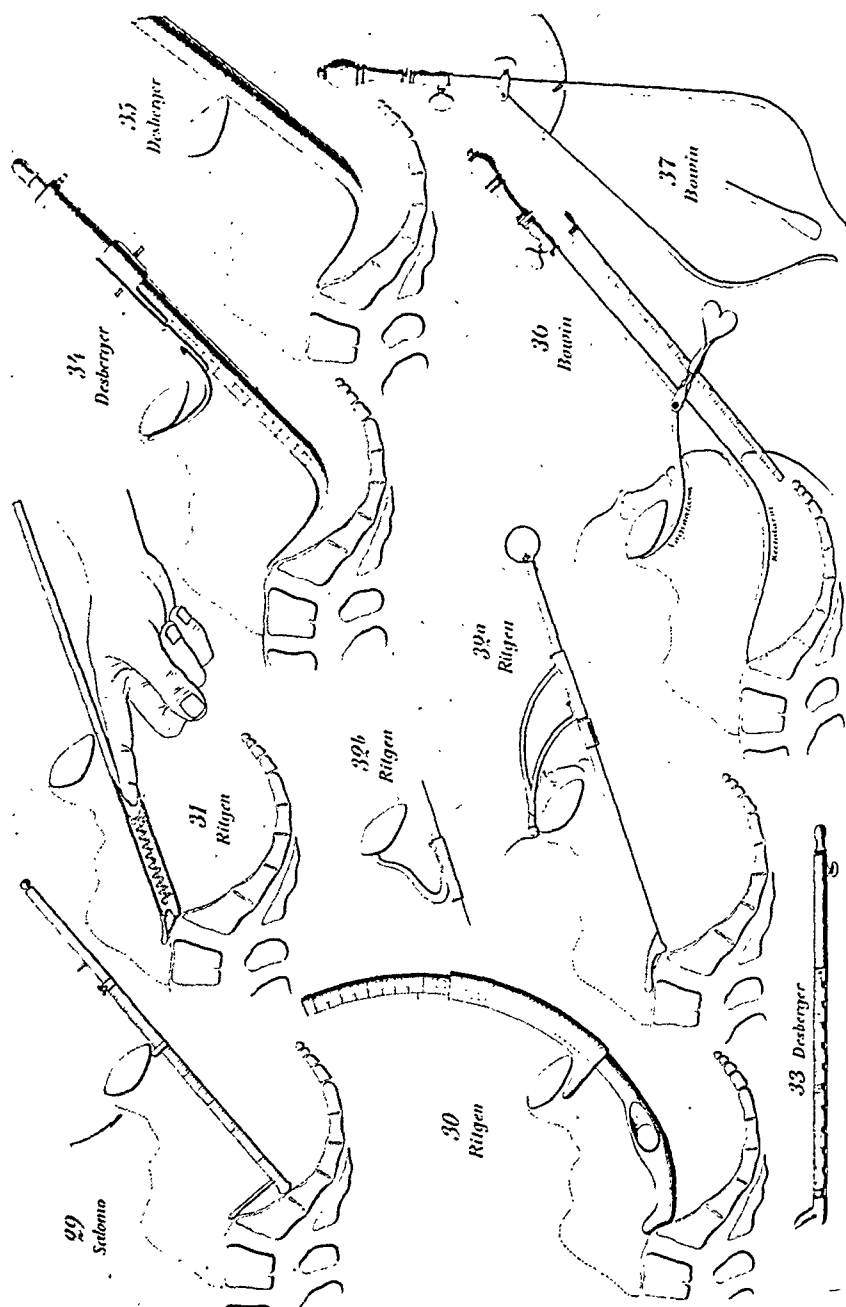
FIG. 10. VARIOUS TYPES OF PELVIMETERS AS ILLUSTRATED BY SKETCH
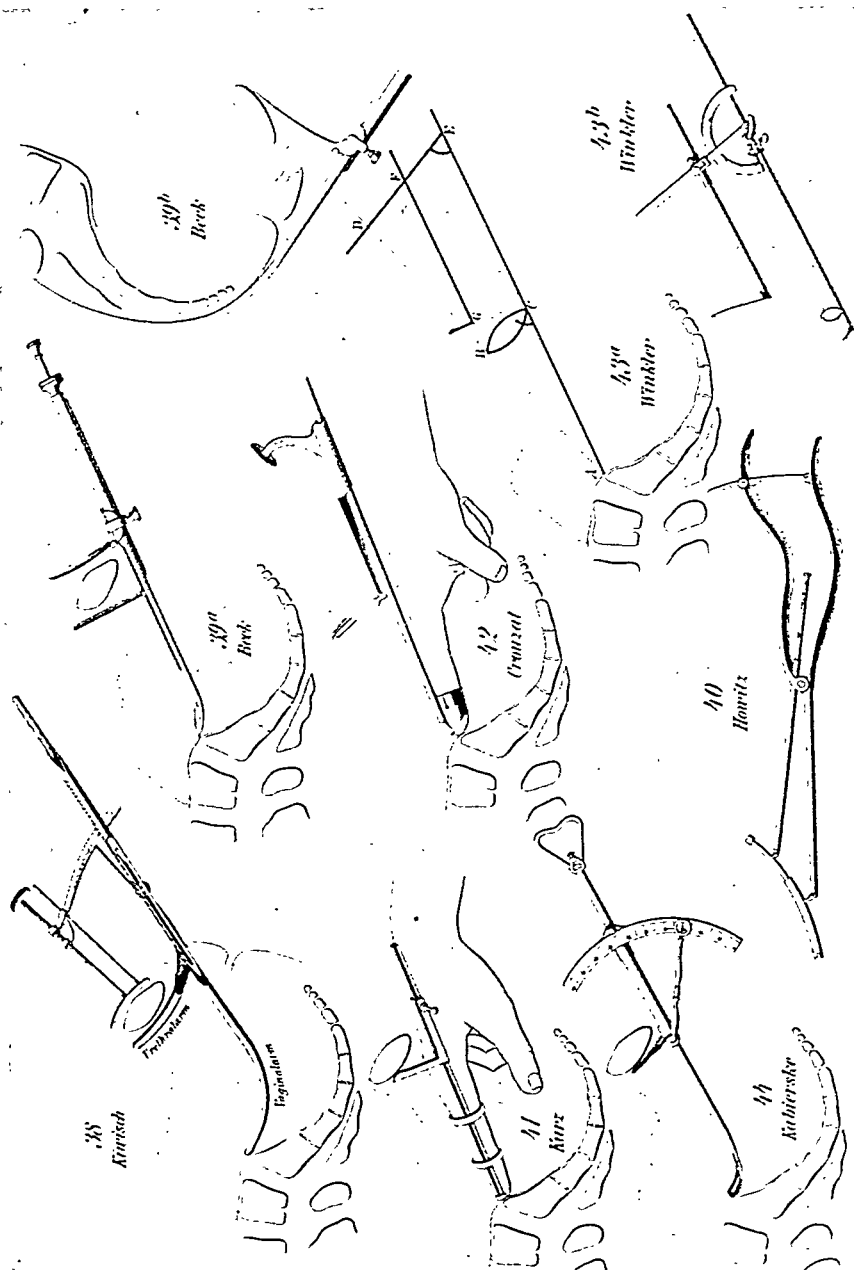
FIG. 11. VARIOUS PELVIMETERS AS ILLUSTRATED BY SKUTSCH
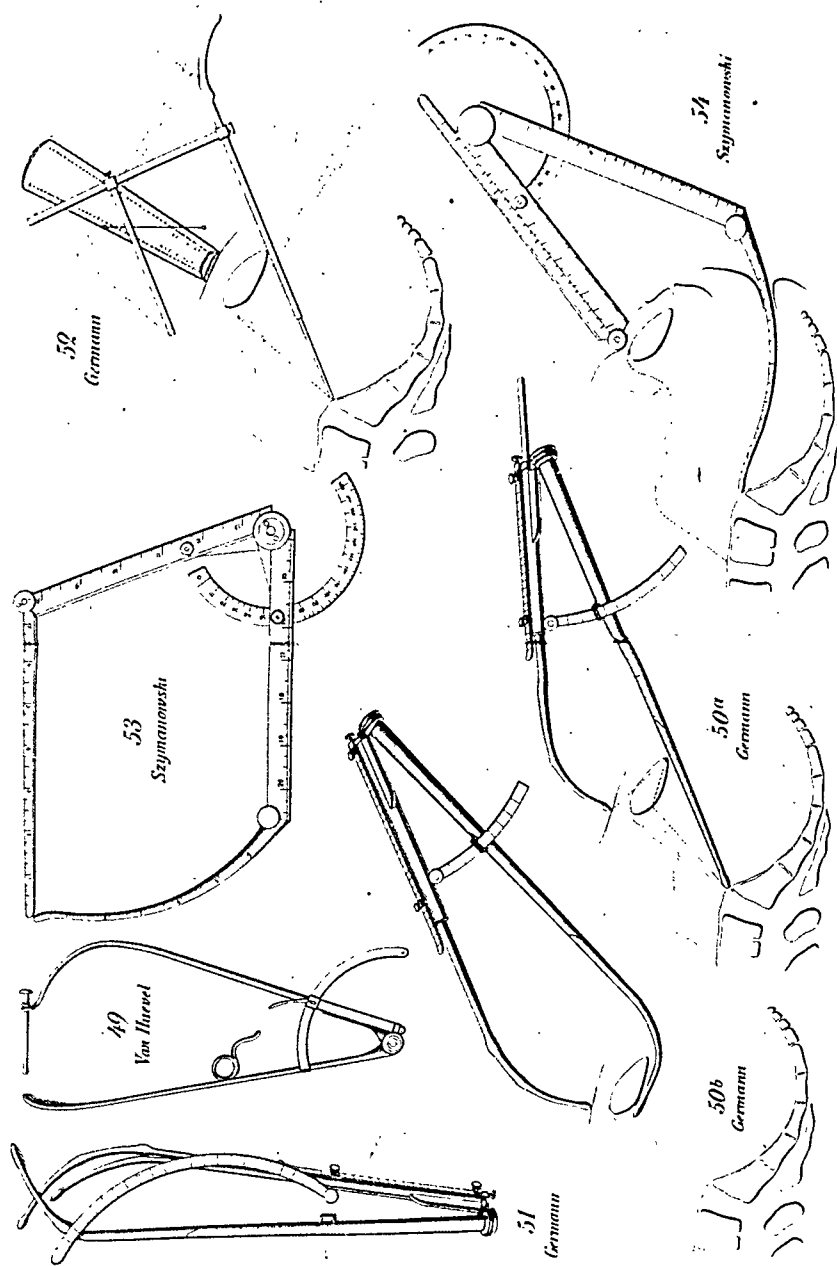
FIG. 12. VARIOUS PELVIMETERS AS ILLUSTRATED BY SKUTSCH
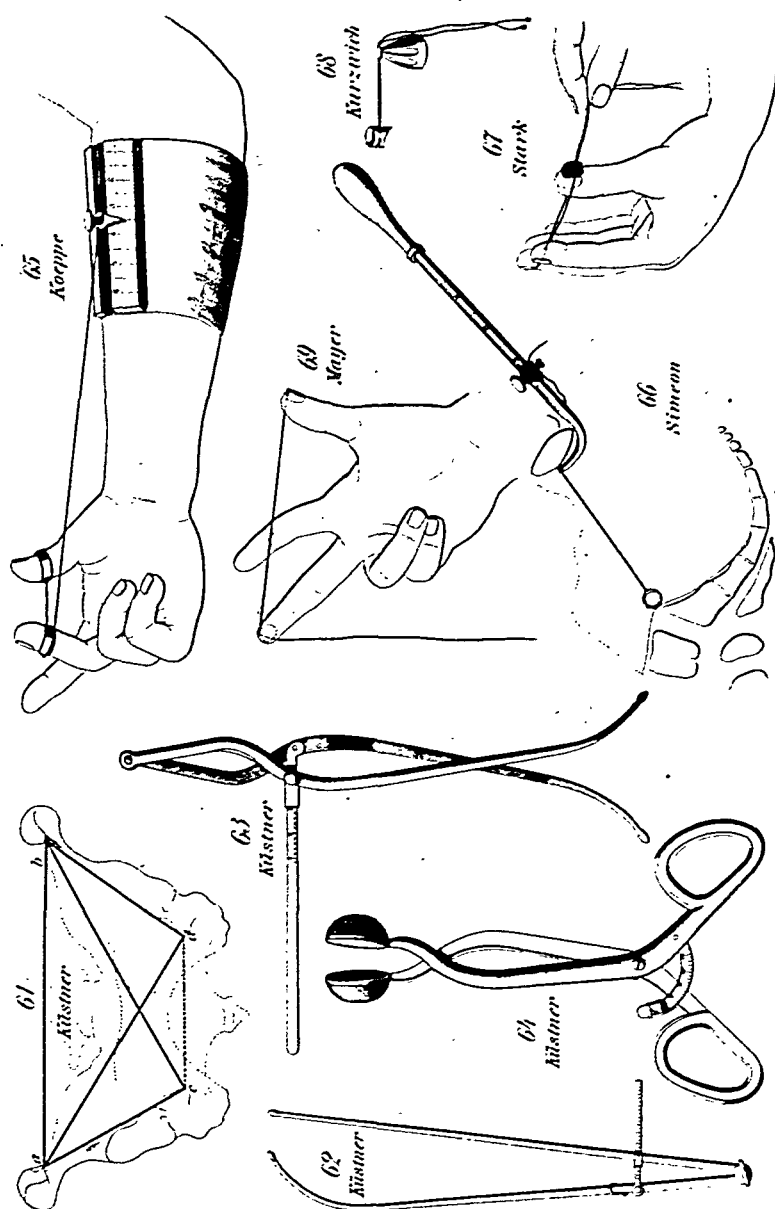
Fig. 13. Various Pelvimeters as Illustrated by Skutsch
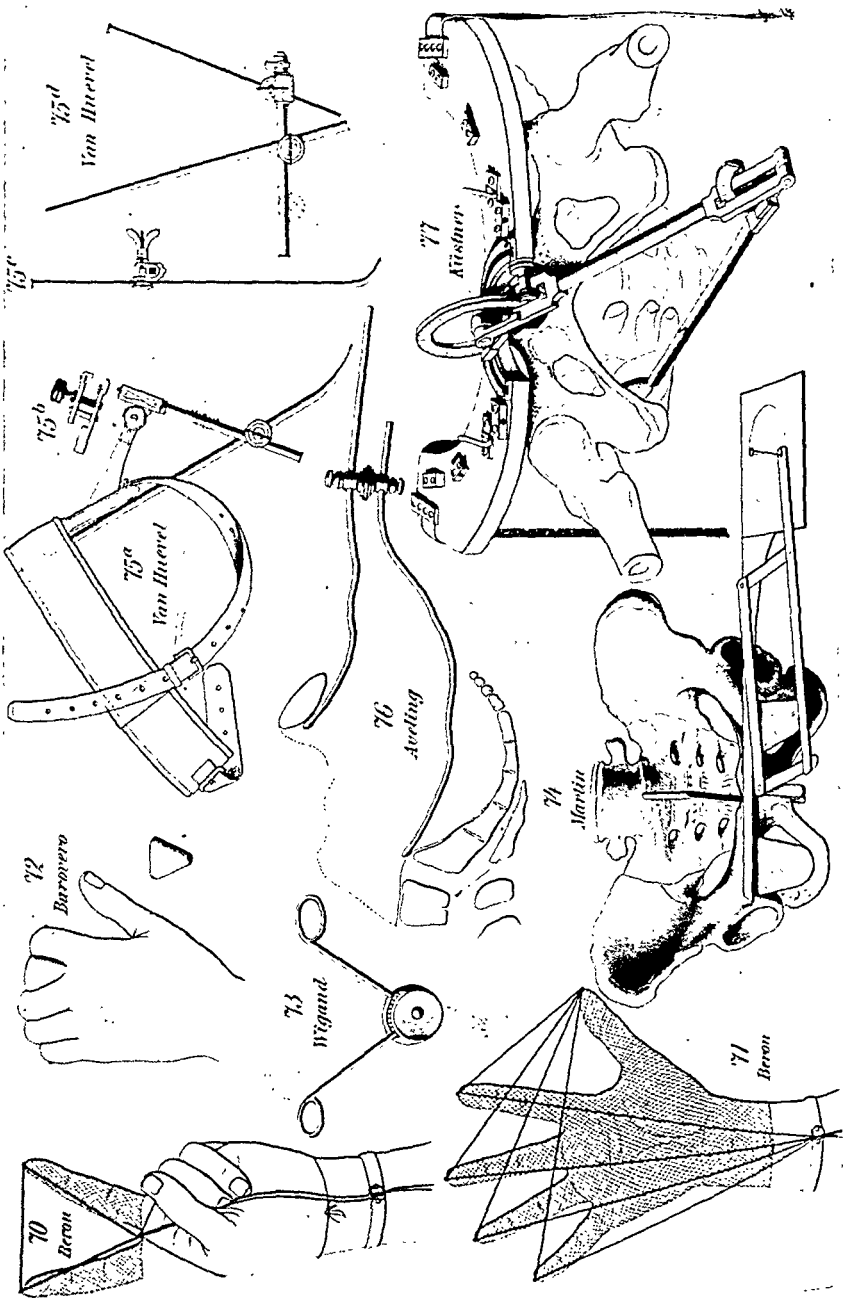
FIG. 14. VARIOUS PELVIMETERS AS ILLUSTRATED BY SKETCH
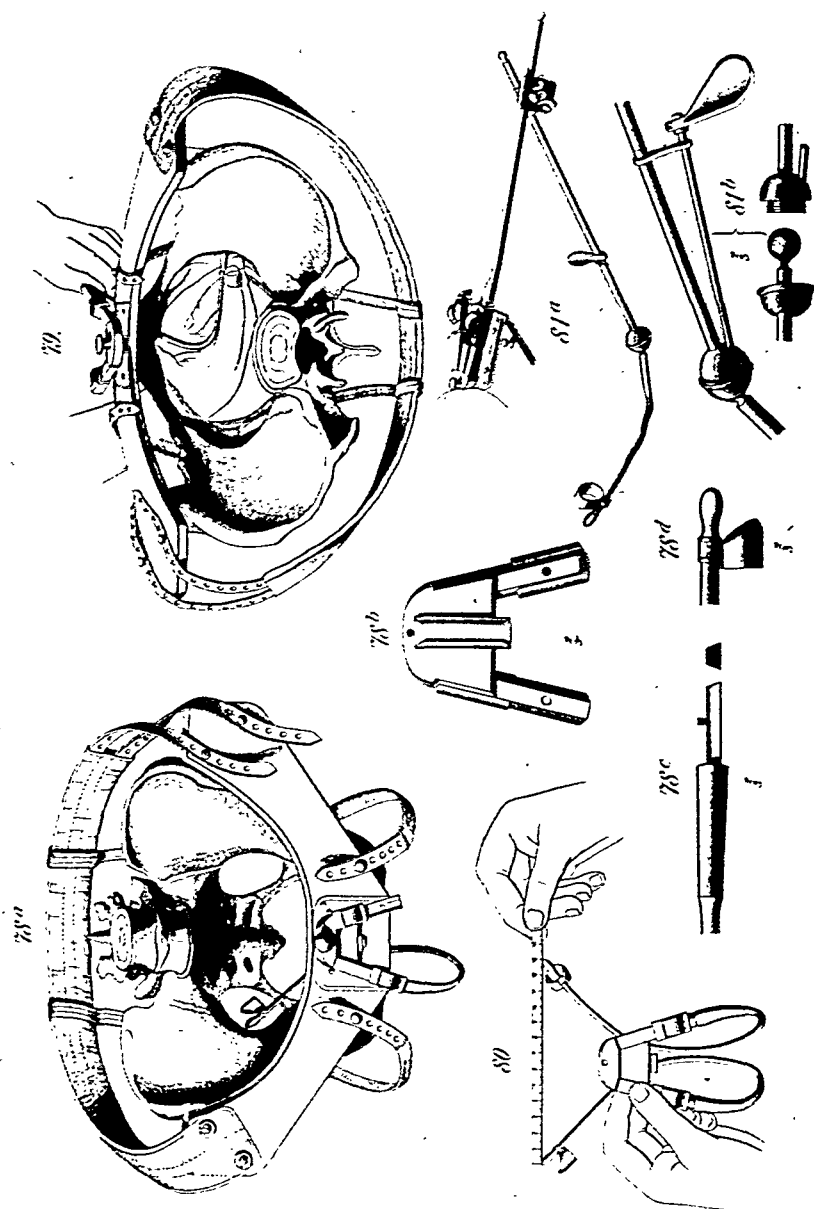
FIG. 15. VARIOUS PELVIMETERS AS ILLUSTRATED BY SKUTSCH

FIG. 16. SKETCH PELVIMETER.
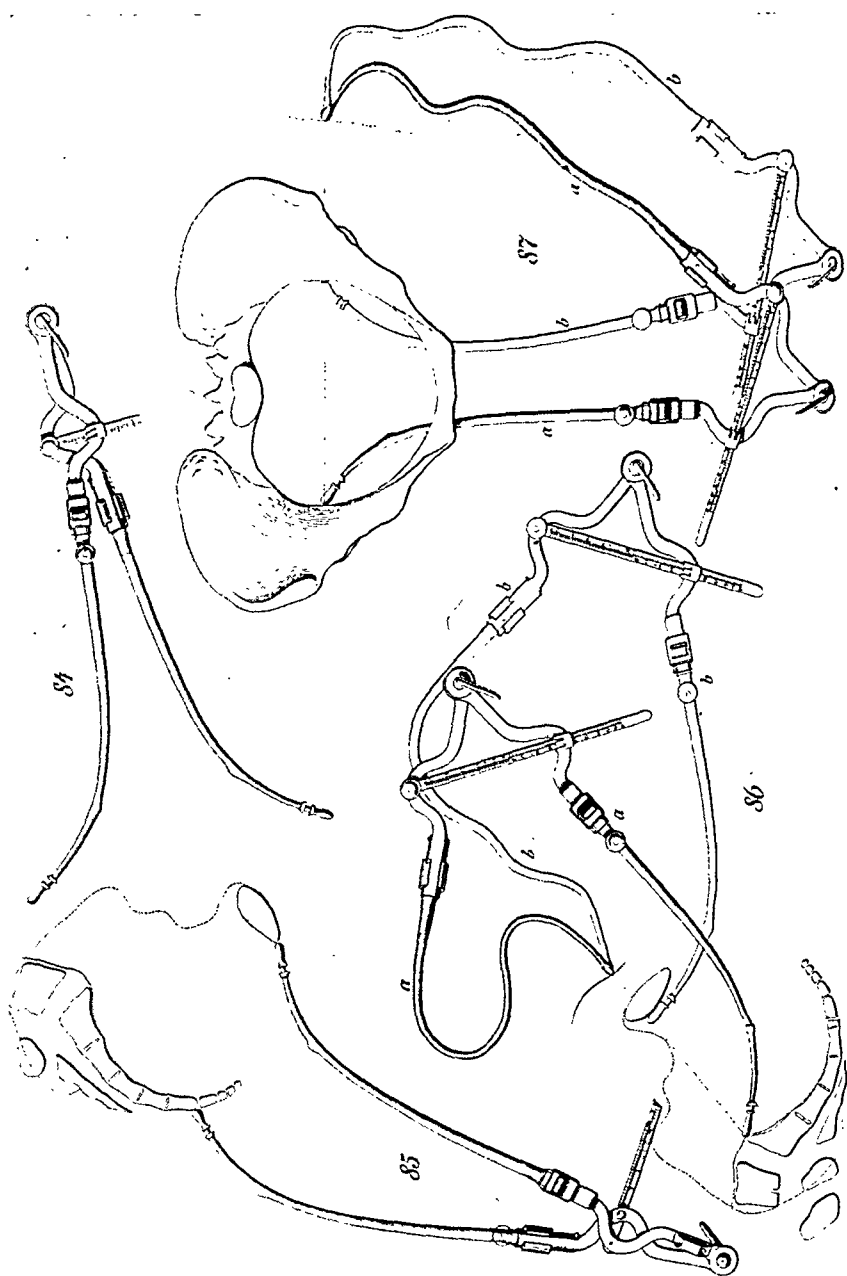
temerity to discontinue the taking of these diameters as well as the external conjugate and have had no reason to regret this step. Moreover, Dr. Greenhill tells me that he expects to delete these external measurements from the next edition of his book. If he does so, his work will probably be the first textbook published in the last 150 years which has not described and recommended these meaningless dimensions.
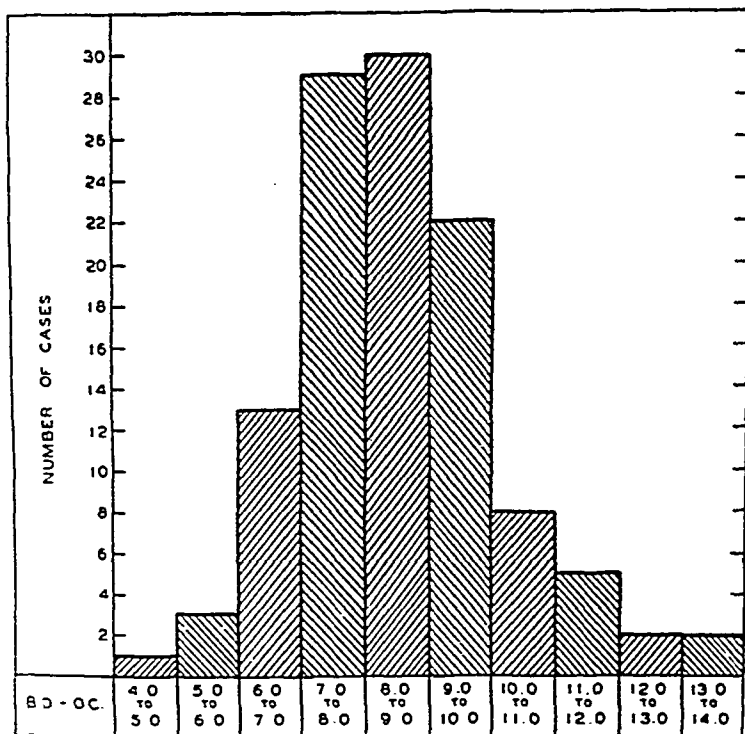
FIG. 17. The distribution of the difference between the external conjugate (Baudelocque diameter) and the obstetrical conjugate (x-ray) in 115 cases. Mean difference is 8.53 cm., least difference 4.93 cm., and the greatest difference 13.5 cm. (Dippel).

Outlet mensuration, likewise, has brought fallacy and disillusion. In Thoms' "The Obstetric Pelvis," published in 1935, he discredited external pelvimetry in general, but at that time believed that manual mensuration of the pelvic outlet was still of value.[20] Recently, however, after a decade more of study and thought, he has reversed his opinion and has reached the conclusion that even these outlet measurements are unreliable,—indeed, about as unreliable as the rest.

Although x-ray pelvimetry was described in 1900, its development and popularity are phenomena of the past two decades. Even today, however, the greatest divergency of opinion exists about its value. Some feel that it is su-

.perfluous and may even be misleading. Others regard x-ray pelvimetry as the panacea for all perplexities in the management of pelvic contraction; and even the opinion is extant that roentgenologists, simply on the basis of films, can prognosticate the outcome of labor in this complication. As is usually true under such circumstances, the truth lies somewhere between the two extremes.

X-ray pelvimetry, in my opinion, is essential to the management of cases of pelvic contraction for several reasons:
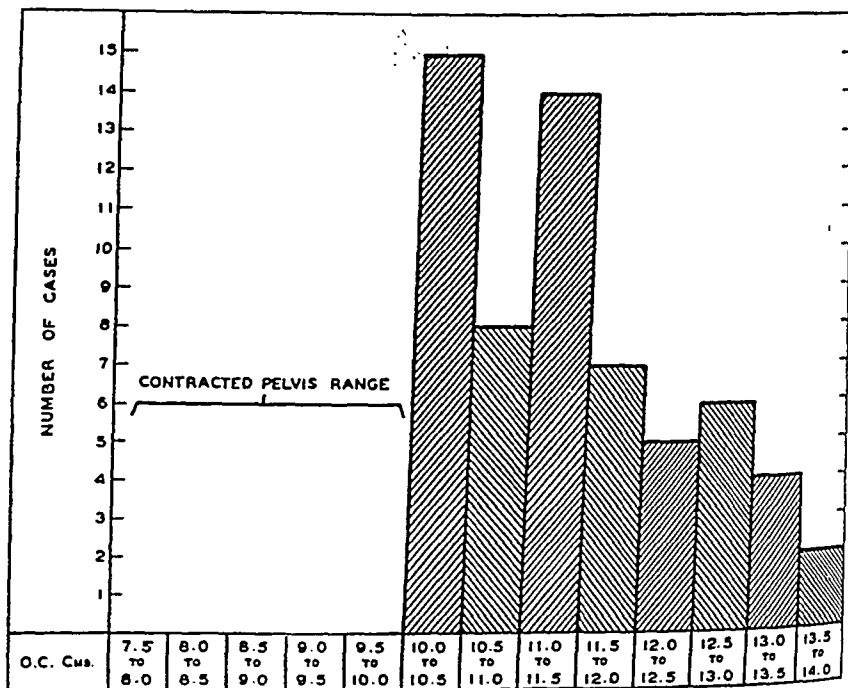
FIG. 18. The distribution of the obstetrical conjugate measurement (x-ray) in 61 cases in which the diagonal conjugate was greater than 11.5 cm. Mean length of obstetrical conjugate is 11.41 cm.; shortest length 10.0 cm.; greatest length 13.72 cm. (Dippel).

1. It provides precision of mensuration to a degree which has never heretofore been possible. The clinical importance of such precision will become apparent when the shortcomings of the diagonal conjugate measurement are considered. It has been our experience that when this diameter exceeds 11.5 cm., the antero-posterior dimension of the inlet is very rarely contracted. Thus as shown in Fig. 18, in 61 consecutive cases in which the diagonal conjugate measurement exceeded 11.5 cm., there was not a single instance in which the obstetrical conjugate fell below 10.0 cm.[18] On the other hand, when the diagonal conjugate is under 11.5, this dimension is not always a reliable index of the obstetrical conjugate since the difference between these two diameters (usually said to be 1.5 cm.) may range between 0.1 and 3.1 cm. (Fig. 19). For instance, we recently had two

primigravidae in our clinic both with a diagonal conjugate of 10.5 cm. In one the obstetrical conjugate was 10.2 and vaginal delivery was easy; in the other it. was 8.2 and cesarean section was obligatory.

2. It provides mensuration of certain diameters which were previously not· easily obtainable, such as the transverse diameter of the inlet and the interischial spinous dimensions. After long neglect the latter measurement is at last receiving recognition as an important cause of midpelvic arrest and of· difficult forceps operations.
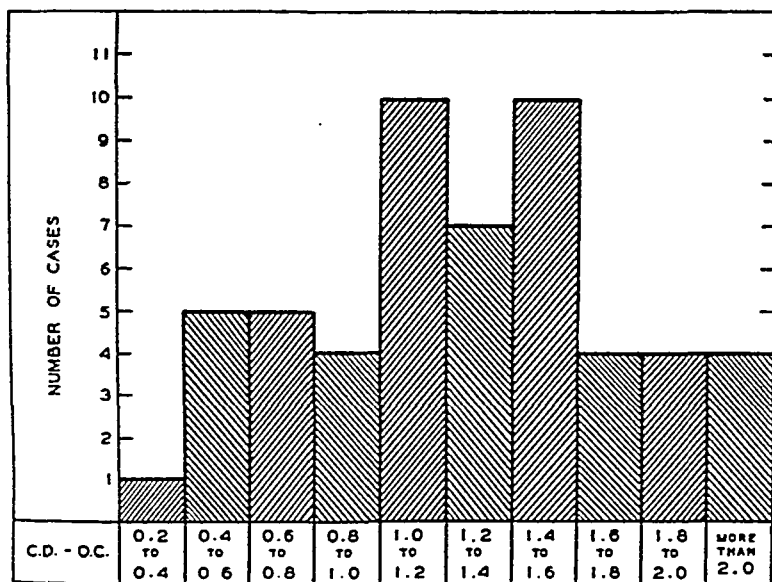
FIG. 19. The distribution of the difference between the diagonal conjugate and the obstetrical conjugate (x-ray) in 54 cases in which the diagonal conjugate measured 11.5 cm. or less. Mean difference is +1.26 cm.; greatest difference +3.14 cm.; least difference +0.10 cm. (Dippel).

3. By the stereoscopic technique, x-ray pelvimetry permits visualization of the general architecture of the pelvis and, in experienced hands, this type of information is almost as valuable as actual mensuration. The clinical importance of pelvic architecture was the great contribution of Caldwell and Moloy to obstetrics.

4. When standing films are taken from time to time in the course of labor, very precise information is obtainable concerning the descent, or lack of descent, of the biparietal plane of the head,—information which is difficult to obtain by palpating the presenting part because elongation of the head may make such digital findings misleading.

These several advantages of x-ray pelvimetry would seem clear-cut and undeniable. Yet—strangely enough, but of this I am certain—the introduction of

this technique has, the country over, been more harmful than helpful to the intelligent management of pelvic contraction. Hence, we are faced with the paradox that this ultra-precise method is to be incriminated as the most recent source of error in this field. This error is to be charged partly to abject reliance on specific pelvic measurements, to the subordination, or even ·to the utter neglect, of the over-all clinical picture. X-ray pelvimetry is a valuable adjunct in the management of patients with contracted pelvis; but it must be regarded as an adjunct only, just as the cardiologist considers the electrocardiogram as a helpful aid in the management of patients with heart disease. Another error which has helped to discredit the procedure is faulty interpretation of pelvimetry films and this—to speak bluntly—is usually attributable to the fact that the busy obstetrician has not had time to acquaint himself with this discipline. It is a discipline which cannot be learned over-night, but requires study, training and experience if its many pitfalls are to be avoided.

And what, in conclusion, are we to learn from this prolonged perpetuation of error in the history of pelvic mensuration? Two deductions, at least, would appear permissible. In the first place, when we recall the many fine intellects which have pursued the study of pelvic contraction only to err, it becomes apparent that the problem is not as simple as it might seem at first glance. Secondly, on the basis of the evidence submitted, it would seem plausible to suspect that an important cause of this long history of error has been neglect of the multiplicity of factors concerned in labor with pelvic contraction. Pelvic measurements are important to know, and to know accurately, but equally decisive in the outcome of a given case are a host of other circumstances: the general architecture of the pelvis, the size and position of the infant, the presence or absence of uterine inertia which is extremely common in these cases, the status of the membranes, the degree of flexion of the fetal head, the presence or absence of asynclitism, the condition of the cervix, the progress in cervical dilatation and in descent of the head over various time limits, the mobility of the head in the pelvis, the Müller-Hillis maneuver, etc. The proper correlation and interpretation of all these findings cannot be expressed in a mathematical formula and come only as the result of long days and nights in the labor room. The ability to evaluate and integrate—warily, circumspectly and correctly—these many phenomena is what we call, of course, obstetrical judgment; and only to such as have garnered that wisdom will the contracted pelvis yield her secrets, so jealously held these many years.

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PATHOLOGY OF PREGNANCY

TREATMENT OF PLACENTA PREVIA

JOHN STURROCK

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While the number of cases of placenta previa admitted to the Royal Infirmary remained fairly constant during the four 5-year periods covered (1926–1945 inclusive), the maternal mortality declined progressively from 9.8 per cent in 1914–1924 and 7.4 per cent in 1926–1930 to 0.8 per cent in 1941–1945. Fetal mortality also fell rapidly in the last 2 periods: from 63 and 67 per cent of the total in the first 2 periods to 56 and 39 per cent in the last two 5-year spans. Fetal deaths after the 36th week dropped from 50 and 55 per cent to 40 and 27 per cent.

In 1926–1930 the vaginal methods of delivery were the accepted treatment, although cesarean section was practiced occasionally. There was a high maternal and very heavy fetal mortality associated with the most frequent approach, that of plugging the lower uterine segment with the half breech.

In the next 5 years more cases were treated by rupture of the membranes or by Willett's forceps. It was being appreciated that minor degrees of placenta previa were often over-treated. Cesarean section was still limited. Maternal and fetal mortality from plugging with the half breech remained high. Blood transfusion was being used more often.

The remaining 2 periods showed a steady improvement in results as the importance was realized of early hospitalization of women with ante-partum hemorrhage, vaginal examinations of such cases only with complete readiness for prompt treatment as needed, and wider indications for cesarean section. The Blood Bank at the Royal Infirmary was established in 1939. Nevertheless there were 2 maternal deaths following plugging the lower uterine segment with the half breech.

Over the 20-year span, hemorrhage and shock were gradually reduced by modern management in all its details. The common pattern in the deaths was plugging with the half breech, efficient in controlling the bleeding at the time, followed within 5 hours of delivery by collapse and death, despite blood transfusion. The shock develops after completion of the third stage even if bleeding is slight, and often seems irreversible. An understanding of the mechanism of these fatalities and their remedy would reestablish confidence in plugging the uterine segment with the half breech in multiparae with very premature children

and in the teaching of this method for those who must practice where no maternity hospitals are available.

Sepsis as a cause of death has been reduced, the sulfanilamides and the considerable limitation of vaginal methods to rupture of membranes and Willett's forceps playing important parts. Fetal scalp traction can often be employed alternative to the half breech and at a lower cost in fetal life.

The 2 maternal deaths in 1941–1945 resulted from severe postpartum hemorrhage and collapse which failed to respond to transfusion in 1 case, and acute terminal heart failure in the other.

Hendry and Baird found the long-term influence of cesarean section to compare favorably with vaginal treatment. In the 20 years covered here there were 40 cases of uterine rupture, in 11 of which a previous cesarean section scar had given away; in 3 of these the indication for section was placenta previa.

A comparison of maternal and fetal death rates in 5 hospitals indicates a very low fetal death rate (23.5 per cent) at Belfast, where Macafee has personally supervised a team treating all cases of ante-partum hemorrhage and has treated hemorrhage conservatively, delaying digital examination of the lower segment. At Edinburgh the reduction in fetal mortality is related to greater use of cesarean section in major cases, avoidance of over-treatment of the minor cases, and improved management of the premature child. In view of Macafee's experience, conservatism must be considered; but the author feels that apart from possible ultimate disappointment because of more frequent congenital fetal deformities associated with placenta previa, such a course places a great demand on urgently needed antenatal beds and on the medical and nursing staff, and even in hospital is not without a risk to the mother of massive and even fatal hemorrhage.

(See editorial note following next abstract.)

TREATMENT OF PLACENTA PREVIA

A REVIEW OF CASES TREATED IN THE GLASGOW
ROYAL MATERNITY HOSPITAL, 1941–1946

A. THE MATERNAL ASPECT

HUGH STIRLING

B. THE FOETAL ASPECT

ROBERT A. TENNENT

Glasgow, Scotland

In this review of all cases of placenta previa admitted to the Glasgow Royal Maternity Hospital in 1941–1946 inclusive, mild cases are those in which the

placenta did not reach to the edge of the internal os when the latter was 1 to 2 fingers dilated; the severe group includes all cases in which the placenta was either over the os, or its margin lay within 1 inch of it.

Berkeley's estimate of an incidence of 1:1000 cases is probably still fairly accurate, although hospital numbers have gone up. This series consists of 505 cases (84 in primigravidae, the remainder multiparae), 222 of them classed as mild and 283 severe, the severe types occurring much more often in multiparae. With increasing age there was a marked increase in severity in both primigravidae and multiparae. The average maturity of pregnancy was very similar for both these groups, 36 weeks in mild cases and 34 weeks in severe cases, but the range was considerable. There was a 10.8 per cent incidence (24 cases) of postpartum hemorrhage in the mild group and 2.8 per cent (8 cases) in the severe group (most of the latter were treated by cesarean section, with consequent control of the uterus and immediate completion of the third stage). In 18 cases the blood loss was severe. In 8 manual removal of the placenta was necessary.

In the total series there were 18 deaths, 3.6 per cent—4 deaths, 1.8 per cent, in the mild group and 14 deaths, 5 per cent, in the severe group. Hemorrhage and shock accounted for 8 cases, including 3 of postpartum hemorrhage; 3 died of puerperal sepsis; 2 of respiratory failure; 3 under anesthesia; 1 died undelivered of acute cardiac failure and 1 undelivered following an incompatible transfusion. Allowing for 1 case of cardiac disease, 1 acute pulmonary edema, and 2 who died within $\frac{1}{2}$ hour of admission, the corrected mortality rate is 2.8 per cent for the whole group.

The overall morbidity rate, including all types of postnatal complications, was 13.7 per cent, the larger proportion among the severe cases. Respiratory infection was responsible for 17 cases, puerperal sepsis for 8; the others were ascribed to wound sepsis, urinary infection, thrombophlebitis, localized uterovaginal sepsis, secondary postpartum hemorrhage, mastitis, and 18 described as pyrexia of unknown origin.

Over half (120) of the mild cases received no treatment, and the next largest number (65) were treated by rupture of membranes. There were 2 deaths in each of these groups, and of these 2 were "unavoidable," giving corrected mortalities of 0.8 and 1.5 per cent. No deaths occurred among the remaining few treated by packing, version, and cesarean section. In the severe group, cesarean section was the most frequently used treatment (252 cases) and easily the best, giving a corrected mortality of 3.2 per cent.

Treatment was defined as "delayed" where it was not carried out within 24 hours. Patients were kept under observation and facilities for immediate treatment were at hand. Where delay was adopted and recurrent or continued hemorrhage 2 or 3 days later made active treatment imperative, the case was included in the delayed group as a failure. For the mild group, corrected mortality was 0.66 per cent for those receiving immediate treatment, 1.4 in the delayed; morbidity 8 and 11.4 per cent. In the severe group, corrected mortality with immediate treatment was 3.7 per cent, with delay 4.5 per cent, and the morbidity 14.8 and 25.4 per cent. Puerperal sepsis was confined to the immediate group.

In general terms, there appears on the basis of these figures to be a slight but definite added risk to the mother when delay is adopted.

There was 1 death each on the operating table under spinal and under general anesthesia, with fatal complications following more commonly after general anesthesia.

Of the 507 infants born in these cases, 65.9 per cent left the hospital alive, 15.2 per cent were stillborn, and 18.9 per cent died during the neonatal period, giving a combined mortality rate of 34.1 per cent. The outlook was much more favorable for those in the mild group. Anencephaly (3 cases) was the only fetal abnormality noted more than once.

The fetal mortality remains very considerable until 6 pounds, when there is a sharp decline from 41.1 to 12 per cent, quite marked in the neonatal death rate and more gradual in the stillbirth rate. Fetal mortality might be improved by trying to insure a birth weight of 6 pounds, increasing survival by better maternal nutrition and better pediatric care, and trying to decrease the stillbirth rate.

Among the 120 infants in mild cases where no treatment was instituted, the stillbirth rate was high, 17.5 per cent, and the neonatal death rate was 12.5 per cent, a total of 30 per cent. Of the 51 under 6 pounds, 33 were born alive, and their neonatal death rate was 39.4 per cent. There were only 2 severe cases who received no treatment; 1 infant was stillborn and 1 survived.

Those 63 mild cases in which membranes were artificially ruptured had the lowest fetal mortality, 24 per cent: 8 per cent stillbirths, 16 per cent neonatal deaths. Among 20 infants under 6 pounds, 17 were born alive, and their neonatal death rate was 41.2 per cent.

Version and bringing down a leg to control bleeding proved fairly satisfactory in 7 mild cases, with a fetal mortality of 28.6 per cent, but in the severe group it offered little hope of fetal survival (23 infants, mortality 100 per cent). In 5 breech presentations in severe cases, the infants were stillborn. Packing was tried in 3 cases; all infants survived.

In the mild cases, placenta previa was not the main indication for the cesarean sections done. In some, placenta previa was accidentally discovered during the operation. There were 27 infants, with a fetal mortality rate of 11.1 per cent. By far the majority of the severe cases were delivered by cesarean section. Among the 257 infants, the mortality was 34.2 per cent. In the 197 delivered within 24 hours, the mortality was 32 per cent, and 94 (86 born alive) weighed under 6 pounds. In 60 infants delivery was postponed over 24 hours and some times up to 7 weeks. Among these, the fetal mortality rate was 41.7 per cent, and 33 infants (31 born alive) weighed under 6 pounds.

For a general picture, all cases were divided into 2 groups, immediate and delayed, according to whether treatment had been started or delivery had occurred within 24 hours of admission. The results appeared generally worse in the delayed group, and delayed treatment on behalf of the child questionable. With about the same per cent of stillbirths, there was a higher neonatal death rate in the delayed group. Of 139 infants in the latter group, 76 (54.7 per cent) failed to reach 6 pounds, while 43.5 per cent of the 368 in the immediate treatment group

weighed under 6 pounds.   In 62 cases, however, pregnancy was continued at least another 7 days.   This no doubt did improve chances of fetal survival, though life in utero with a placenta previa which is bleeding or has bled is probably not comparable with that in normal pregnancy.

On the whole, in this series, the obstetricians tended to interfere when there was a recurrence of the bleeding, in contradistinction to Macafee, who states that latterly numerous small recurrent hemorrhages in a patient under observation cause no serious anxiety.   (Macafee reported maternal mortality of 0.57 per cent and fetal mortality of 23.5 per cent in the British Journal of Obstetrics, August 1945.)   Macafee states there is a "theoretical" possibility of sudden severe hemorrhage in a multipara apart from vaginal examination; 1 patient in this series died of such hemorrhage.   The authors feel that fetal survival is at least no more certain in the delayed than in the immediate group, and that delay in treatment of placenta previa does increase the maternal risk.   Their Glasgow patients, who will probably have several future pregnancies and who suffer from varying degrees of anemia and malnutrition, can be spared extra risks and strain by prompt diagnosis and immediate treatment in case of placenta previa.   Expectant treatment, they feel, should be reserved for elderly primigravidae and women with no living children.

Discussion centered around expectant versus immediate treatment, with secondary remarks on classical cesarean section versus lower segment and on spinal versus general anesthesia.   9 tables.

(These two articles on placenta previa, which summarize large experiences with the condition in Edinburgh and Glasgow, are instructive from several points of view.

In the first place they call to mind the fact that our methods of grading the various degrees of placenta previa are inconsistent and confusing. Thus, in Stirling and Tennent's original paper (abbreviated in first paragraph of abstract) the authors state that "mild cases are those in which the placenta did not reach to the edge of (or overlap in any way) the internal os, when the latter was 1 or 2 fingers dilated; the severe group includes all cases in which the placenta was either over the os, or its margins lay within one inch of it. The mild group therefore corresponds to *lateral placenta previa*, and the severe group includes the *marginal*, *complete* and *central* types." The general thought of the authors here is fairly clear as long as they stay away from the terms *lateral*, *marginal*, *complete* and *central* types. However, if some assiduous student should consult our 3 standard American textbooks and endeavor to check the authors' meaning on the basis of these terms, he would end up in a state of bewilderment for the following reasons:

Stander states that *lateral placenta previa* is synonymous with *partial placenta previa*, being that condition in which the placenta encroaches more or less upon the internal os, but *does not completely cover it*. Quite obviously, Stirling and Tennent regard *lateral placenta previa* as something quite different since it represents their mildest variety, "one which did not reach to the edge of (or overlap in any way) the internal os". The DeLee-Greenhill book gives still another definition, as follows: "When the edge of the placenta is felt at the internal os it is called *lateral placenta previa*." From this statement and the accompanying illustration, it seems clear that their intention is to designate as *lateral* that degree of the complication which Stander, Beck and others call *marginal*, but DeLee and Greenhill state that they agree with Solomons that the term *marginal placenta previa* should be discontinued. Beck does not mention the term *lateral placenta previa*.

A Scotch or British student would likewise be confused by the above terms. If the

former consulted the 11th Edition of "A Textbook of Midwifery" by Dr. R. W. Johnstone, for many years Professor of Midwifery and Diseases of Women in the University of Edinburgh, he would find that that standard Scottish textbook states that *lateral placenta previa* is synonymous with *partial placenta previa* and is "one whose edge partially overlaps the os," again, a different understanding of the term than that of his Glasgow countrymen. If a British student looked up the term in "Ten Teachers' Midwifery," he would find 3 types of the condition described, the *complete* variety and 2 gradations of *incomplete*, with the additional statement that "The old terms central, lateral and marginal have been discarded as they give rise only to confusion."

By way of exonerating Stirling and Tennent in this matter it should be noted that they employ the customary terms only by way of amplifying their definition of *severe* and *mild* types and, like "Ten Teachers' Midwifery," find the traditional names variously defined and confusing.

But if it be true that usage of these old terms lacks uniformity and has led to misunderstanding, what can be done about it? As for the term *lateral*, I find difficulty in discovering much justification for its employment despite the fact that DeLee and Greenhill apparently prefer it to *marginal*. In the first place, it lacks the descriptive advantage of the latter name; secondly, the placenta is rarely located on the lateral uterine wall but on either the anterior or posterior, and in a sense, then, the term is incorrect; thirdly, from the viewpoint of expediency, if the term *lateral placenta previa* could be discarded, much of the confusion would be eliminated. We would then have: 1. *Low implantation of the placenta*, in which the placenta can be touched by the examining finger but does not extend as far down as the margin of the internal os; 2. *Marginal placenta previa*, in which the placenta just reaches the margin of the internal os; 3. *Partial placenta previa*, in which the placenta overlaps part of the internal os and 4. *Complete, or central placenta previa*, in which the placenta covers completely the internal os. Of course, the objection may be raised that all these definitions are vitiated by the fact that they are relative to the degree of cervical dilatation, but since most cases of placenta previa start to bleed at about 2 cm. dilatation and hence are ordinarily examined at that stage, the relationships would be constant and suitable for comparison with other cases in the majority of instances.

A few years ago Professor F. J. Browne of London suggested classifying placenta previa as grades or types 1, 2, 3 and 4, in correspondence with the numerical designations in the preceding paragraph. Although these numerals would have no descriptive value, they possess other advantages and, if I am not mistaken, this terminology is gaining ground in Great Britain where dissatisfaction with the old nomenclature has been voiced more loudly than in this country.

Turning now to some of the more practical issues discussed in these papers, I cannot escape the impression that their authors still regard "plugging with the half-breech," or Braxton Hicks' version, with a certain nostalgic longing. As for Sturrock's question about the mechanism of the fatalities which occur so often within 5 hours of delivery following this maneuver, a rather convincing reply to his query, it seems to me, may be found in Hitschmann's classic monograph published in Vienna in 1921. On the basis of an exhaustive analysis of over 5000 cases of placenta previa culled from the German literature, he found that the most common cause of death in placenta previa was not "placenta previa bleeding" (bleeding due to separation) but to bleeding consequent upon trauma to the cervix and lower uterine segment inflicted in the course of Braxton Hicks' version, bagging, etc. Many subsequent observations have confirmed his findings. It has been insufficiently emphasized that it is this extreme friability, vascularity and general vulnerability of the lower segment in placenta previa which underlie the rationale of abdominal delivery in this complication. In regard to the management of placenta previa in the home, far away from maternity hospitals, I have long had the feeling that the best results will be achieved if these patients are transported *untouched* to a hospital even though it be 50 or 75 miles distant. If we have learned anything from the experience of Herman Johnson and of Macafee with the temporizing treatment of placenta previa, it is that the first hemorrhage is rarely, if ever, fatal

provided no internal manipulation has been carried out and, by the same token, that there is plenty of time for such transportation. This application of Johnson's and Macafee's teachings to the management of placenta previa in the home has not received the consideration it deserves.

But the patient must be "untouched,"—and this applies to rectal examination as well as to vaginal. In a report by Simon Brody in the February, 1948 issue of the American Journal of Obstetrics and Gynecology, p. 359, the history of a fatal case of placenta previa is presented which the author believes refutes the contention that women do not bleed to death from placenta previa without cervical manipulation. But even a cursory reading of Brody's case will make it plain that his patient did have cervical manipulation because she had a rectal examination upon admission to the hospital; and it was a few minutes thereafter that she suffered a profuse, fatal hemorrhage. From the viewpoint of causing further separation of a placenta previa, cervical manipulation per rectum can be just about as effective as per vaginam.

It is the contention of both these papers that temporizing in placenta previa has many drawbacks and hazards and should be reserved for elderly primigravidae and women with no children. It is good to have this point of view expounded because it will serve to curb excess enthusiasm over the expectant method of treatment, especially unwarranted attempts to carry placenta previa patients to term despite repeated hemorrhages. On the other hand, the figures which the authors present to document their thesis do not seem especially convincing. Although they interpret their data as indicative of a slightly higher maternal mortality in the "delayed treatment" group, the difference between the "delayed" and "immediate" treatment categories is not statistically significant. To their analysis of fetal outcome and their conclusion that "fetal survival is at least no more certain in the delayed than in the immediate group," I would object emphatically. I say this because it is manifestly unfair to compare fetal outcome in these two categories because, inevitably, the immediate treatment series would be heavily weighted with cases in which the first bleeding occurred near term; in these patients there would be no reason for delay and the babies, being larger, would naturally have a better outlook. Contrariwise, the delayed treatment group would necessarily be made up in large measure of cases in which the first bleeding occurred 6–10 weeks before term and, even with temporizing, we could not expect the overall results to be as good as in cases in which the first bleeding occurred near term.—Ed.)

CHILD-BEARING AND TUBERCULOSIS

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J. T. Jones

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In his experience with the special maternity unit for tuberculous women at Black Notley, treating a total of 260 patients, 75 of whom had active pulmonary tuberculosis on admission, Cohen has become convinced that it is difficult to justify termination of pregnancy on medical grounds alone.

It is possible but not proved that some benefit may appear from pregnancy;

but the contention that a "flare-up" is particularly likely soon after delivery is disputed at Black Notley, where fewer cases break down after delivery than would be expected within the same time in the natural course of the disease irrespective of pregnancy. The effect of diaphragmatic level has been greatly exaggerated. The breakdowns that do occur are due to such factors as the strain of caring for the infant, overwork, financial hardship, etc. In other words, the indications for abortion are really social, which raises medico-legal questions. As others have concluded, the necessity must be established in each individual patient.

Jones mentions that tuberculosis runs such a variable course that it is almost impossible to provide reliable controls. However, he is primarily interested in the practical factors other than pathological lung changes. The present-day overcrowding is a well-known factor in spread of tuberculosis. In 1929 the death rate in children under 5 from non-pulmonary tuberculosis was 14 times greater in a home where there was open tuberculosis than in a normal one; it would be probably higher under today's living conditions.

At the 2 extremes there are the patients who fail to take even elementary precautions against the spread of infection, and the over-anxious mothers whose worry about infecting the child places an added burden on their general health. Prolonged ante- and post-natal institutional treatment is advocated, but with present staff and bed shortages is impossible. Lack of domestic help, added financial strain, and sleepless nights all help undermine the patient's already devitalized system.

All these factors and many others need careful consideration before final condemnation of abortion in tuberculosis cases.

(This is a clear, concise and forthright statement about which the majority of us would agree. The whole problem was discussed in extenso in an editorial note in the Survey 2 years ago (1: 485, 1946) and it suffices to add here that institutional accommodations for tuberculous pregnant women are still woefully lacking in most states. Since everyone agrees that institutional treatment is essential in the presence of activity, it is this lack which forces our hand in the direction of abortion more often perhaps than any other factor. Of the pregnant women who pass through my own clinic with active pulmonary tuberculosis, about ½ are aborted,—in large measure because institutional management is not feasible.—Ed.)

PROPYLTHIOURACIL IN PREGNANCY: REPORT OF A CASE

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Although the anti-thyroid drugs, particularly thiouracil, have been used extensively for the control of hyperthyroidism and have been adequately re-

ported, there has been little in the literature concerning their use in pregnancy. The author reports an unusual case of a 38 year old 253 pound colored female, para 3, gravida 5, whose prenatal course was complicated by hypertensive cardiovascular disease and thyrotoxicosis. The patient was admitted to the hospital in the 8th month of her pregnancy with a blood pressure of 220/120 with 3+ edema which was generalized. She was also vomiting occasionally. For the past 2 years the patient had noticed thyroid enlargement but with no toxic symptoms until this pregnancy. On physical examination there was no exophthalmos but the thyroid gland was diffusely enlarged, being larger on the right than on the left. The heart was clinically enlarged with a rapid rate and regular rhythm. A systolic murmur was heard in the aortic area. Marked rales were heard at both lung bases. Fetal heart tones could not be heard nor the position of the fetus determined by rectal examination. The admission diagnosis of nonspecific toxemia of pregnancy, hypertensive cardiovascular disease with cardiac failure and thyrotoxicosis was confirmed by medical consultation. The patient was digitalized with digitoxin and given the routine measures for cardiac failure. Lugol's solution 10 drops t.i.d. was started on the night of admission and 3 days after admission propylthiouracil, 50 mg. t.i.d. was begun. Three days after the institution of propylthiouracil therapy marked improvement was noted. The blood pressure had fallen to 150/100, the edema had substantially cleared, dyspnea was relieved and the rales in the lung bases had disappeared. The pulse rate, however, was still high, ranging from 100 to 120 daily. The patient was maintained on digitoxin .3 mg. alternated with .2 mg. daily, salt free diet, fluids ad libidum, Lugol's solution 30 drops daily, and propylthiouracil 150 mg. daily. The basal metabolic rate on this therapy fell from +74 to +54 and the blood cholesterol increased from 156 mg. per cent to 294 mg. per cent. One month after admission the patient was considered at term and in good condition. A castor oil and enema induction of labor was attempted with no results. Three weeks later a pitocin induction was attempted which produced only mild to moderate pains. Ten days later another pitocin induction produced fair mechanism of labor which gradually became stronger and 4 hours later she delivered spontaneously and without complication a 7 pound 4 ounce male infant. Resuscitation with tracheal catheter and oxygen for 10 minutes was required. Examination of the baby 24 hours later and again 48 hours later revealed a normal looking and reacting colored male infant. Physical examination was negative and no thyroid enlargement could be detected.

(See editorial note following next abstract.)

THIOURACIL IN THE TREATMENT OF HYPERTHYROIDISM COMPLICATING PREGNANCY AND ITS EFFECT ON THE HUMAN FETAL THYROID

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J. Clin. Endocrinol., 7, 767–773, November 1947

In 10 cases reported in the literature in which thiouracil has been used for pregnant women, there was only 1 in which the child's thyroid was enlarged at delivery and remained so for several months.

Experimental studies have shown that thiouracil does pass through the placenta in rats and that repeated doses to newborn rats can induce cretinism. Goldsmith recorded that newborn rats whose mothers had received thiourea daily were normal in weight and external appearance; the thyroid was slightly increased in weight and there was active hyperplasia characterized by high columnar epithelium with a limited amount of stainable colloid, but these effects disappeared when the animals were placed on a laboratory stock diet.

The thyroid is probably fully functioning in humans at birth. Follicular-like structures are not present in the fetus before the 5th month. Colloid has been demonstrated in the 6th month and first evidences of secretion into the individual follicles in the 7th. Some feel that the mother's hormone, passing through the placenta, is available to the fetus, since infants born with or without atrophic thyroids exhibit no symptoms of cretinism though they soon manifest a latent athyreosis. The transversal of thyroglobulin is denied by others, as in Dorff's study of 2 sets of twins in which 1 twin in each set was a sporadic cretin. Since the onset of sporadic cretinism is insidious and rarely recognizable before the third month, it is important to know whether thiouracil can induce cretinism in the human.

Toxic hyperthyroidism is an uncommon complication of pregnancy, the reported frequencies ranging from 0.008 per cent in 1 series of 100,000 pregnancies to 3.7 per cent in a series of 937. The majority of reports show less than 0.1 per cent.

The author treated 3 pregnant hyperthyroid women with thiouracil. One aborted at 3 months, although her basic metabolism was normal. The second delivered at term a normal baby whose thyroid showed no enlargement. In the third case, a markedly toxic hyperthyroid woman in the 26th week of pregnancy, thiouracil used up to and through delivery brought the basic metabolic rate down to normal and maintained it. Dosage was 0.6 gm. per day for 1 week, followed by 0.4 gm. per day for 13 weeks. At the time of delivery patient was free of toxic symptoms. An anencephalic monster was delivered whose thyroid gland fell within the normal range in weight (approximately 1 gm. or slightly more in the wet, fresh state) and iodine content. In histological examination the gland had

a moderate amount of colloid and gave little indication of having been subjected to prolonged thiouracil medication.

It appears that thiouracil administered to the hyperthyroid pregnant female does not exert enough injurious influence on the thyroid of the newborn to be detected either microscopically or chemically. This agrees with findings in rats reported by Freiesleben and Kjerulf-Jensen (J. Clin. Endocrin., 7, 47–51). 3 tables, 2 figures.

(In spite of such statements as the above, it may be just as well to postpone final judgment on the safety of thiouracil in pregnancy until more data have been accumulated. For various reasons, which may or may not be sound, we are inclined to stop thiouracil therapy several weeks before term in order to allow any possible changes in the fetal thyroid to return to normal before delivery.—Ed.)

SICKLE CELL ANEMIA IN PREGNANCY

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Sickle cell anemia is a hereditary familial form of chronic hemolytic anemia peculiar to Negroes. The infrequent appearance and unfavorable prognosis of this condition during pregnancy warrant the reporting of 6 additional cases. It is believed that sickle cell anemia decreases the fertility of the female and the severe anemia may be a cause of the increased incidence of abortion, for about 33 per cent of the pregnancies terminate by this means, while another 10 per cent of patients give birth to macerated stillborns. There is no specific treatment for this disease. Blood transfusions have little or no value and are frequently followed by severe reactions.

Six well authenticated cases of sickle cell anemia are presented which were followed through 7 pregnancies. There was 1 maternal death which occurred 12 hours after delivery and autopsy revealed bilateral medullary abscesses extending into the renal cortices, this being ascribed to overwhelming renal infection. There was 1 stillborn infant and 1 neonatal death, the latter being premature, weighing 4 pounds and 2 ounces. The remainder of the infants were viable and normal. One postpartum hemorrhage and 2 severe crises due to sickle cell anemia were encountered in this series of cases. The importance of differential diagnosis of anemia in the Negro race is stressed.

(Our experience with sickle cell anemia in pregnancy has been rather more favorable than that of most authors since we have followed 12 authentic cases through pregnancy and labor with no maternal deaths. In contradistinction to the above authors, we are certain that blood transfusions in these cases do a great deal of good and may be life-saving. The

average number of transfusions given during the course of our 12 pregnancies exceeded 5; and 1 patient had 9. All our patients had hemoglobin levels at one time or another below 50 per cent and in 1 woman the figure was 14 per cent when she was first seen. In the face of such degrees of anemia, what else can one do but transfuse? It is true that reactions are more common in the presence of this disease, but the reactions in our series (20 per cent) have not been alarming.—Ed.)

RETROVERSION OF THE UTERUS

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The author having begun to suspect several years ago that retroversion of the uterus was not a frequent cause of miscarriage, analyzed 674 consecutive obstetric cases in the practice of his partner and himself. Of the 674 cases, 325 were examined before the fourth month, by which time the retroverted uterus has either risen out of the pelvis or become incarcerated. Among these 325 cases examined before the fourth month, the uterus was in normal position in 271 ($83\frac{1}{3}$ per cent), and in retroversion in 54 cases ($16\frac{2}{3}$ per cent). Among the 271 cases with the uterus in normal position, there were 37 miscarriages or abortions (13.6 per cent), while among the 54 cases with retroversion there were 6 miscarriages or abortions (11.6 per cent). None of these cases became incarcerated.

No definitive conclusions can be drawn from so small a series of cases; furthermore, it is not known how many patients miscarry before consulting a doctor. However, this series would seem to indicate that when at the first examination the uterus is found to be retroverted, there is no cause for alarm. For many years the author has made no attempt to replace the retroverted pregnant uterus, except to demonstrate to the patient how to assume the knee-chest position, and the results have been just as satisfactory as when the uterus was replaced and a pessary inserted.

(Brackett's observations are in keeping with opinions expressed in an editorial note on page 26 of the February, 1948 issue of the Survey and I am sure his general contention is correct.—Ed.)

PATHOLOGY OF LABOR AND PUERPERIUM

SHOCK IN OBSTETRICS

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To the clinician there is a group of cases characterized by circulatory deficiency with low blood pressure, decreased blood volume, decreased cardiac output and increased concentration of blood that presents a common clinical picture and may be called shock. At one time it was customary to attribute a certain number of sudden deaths during or after labor to shock. However, it is now clear that the great majority, if not all of these cases will reveal some condition at autopsy sufficient to account for the fatality.

In 1943, in the Province of Ontario, there were 82 maternal deaths with clinical evidences of shock. Of these 33 deaths were due to pulmonary embolism, 31 to hemorrhage, 10 following difficult operative delivery, 5 due to rupture of the uterus, 1 to acute dilatation of the stomach and 1 to severe hypertension.

For the period 1931 to 1943, there were 199 cases of shock in 12,749 deliveries on the public ward service of the Toronto General Hospital. Of the total number of the cases with shock 9 had a blood loss more than 1000 cc. and showed signs of severe shock. In this group there were 6 deaths. Two of these were cases of placenta previa. Both cases had immediate transfusion and were treated by version. Both died following postpartum hemorrhage. The third patient had a large baby with a labor of 44 hours and a difficult forceps delivery. Death was sudden and intrapartum. There was no external evidence of hemorrhage and there was no autopsy. The fourth patient had essential hypertension, delivered spontaneously in 12 hours and had a manual removal of the placenta followed by progressive shock and death in 3 hours. The fifth case was one of a normal pregnancy with spontaneous delivery and a postpartum hemorrhage, followed by progressive shock and death despite transfusions. The sixth case was a normal pregnancy with a breech delivery followed by a severe postpartum hemorrhage and death.

The following factors play an important part in the development of shock: (1) During pregnancy there is an increase in the blood volume but with delivery there is an inevitable loss of blood which may more than overcome the increased volume of pregnancy. The great increase in the size of the uterus full of large blood sinuses results in an organ capable of holding a considerable volume of blood when it is relaxed and its relaxed condition after being emptied provides a fertile source of hemorrhage into the uterine cavity. (2) Disturbance of water

balance which is usually the first indication of toxemia is probably evidence of increased permeability of the capillaries and this of course is one of the essential factors in the mechanism of shock. Toxemia patients with systemic edema withstand trauma poorly. (3) The late toxemias of pregnancy are accompanied by an elevation of blood pressure. After delivery there is often a very sudden drop in pressure which is conducive to the onset of shock. (4) Immediately after delivery there is a marked lowering of intra-abdominal pressure which probably results in dilatation of the splanchnic blood vessels. This lowering of intraabdominal pressure occasionally results in distention of the small bowel of such a degree as to simulate paralytic ileus and probably renders the patient more susceptible to shock.

In the opinion of the author from the clinical point of view the great majority of cases of obstetric shock are directly proportional to the amount of blood loss. In enumerating the causes of shock due to obstetrical mishaps, hemorrhage is probably the most important. The hemorrhage may be slow and prolonged or sudden and rapid but in either case the blood loss may be sufficient to result in shock. From clinical observation it would appear that a patient suffering from rapid loss of a considerable amount of blood responds to therapeutic measures better than one who has lost a comparable amount over a longer period of time. In accidental hemorrhage blood loss may be equal to that from severe placenta previa but in many instances the shock is out of proportion to the observed blood loss. This is true in cases of couvelaire uterus or toxic uteroplacental apoplexy in which there is an infiltration of the uterine wall with blood separating the muscle bundles and producing a ligneous, noncontracting uterus. To this is added the fact that all of these patients are suffering from severe toxemia. Finally there is postpartum hemorrhage which is of 2 types, that following trauma with tearing of the birth canal, and bleeding due to failure of an atonic uterus to contract and shut off the blood sinuses. In most instances the hemorrhage is external and therefore apparent, but occasionally, when it results from injury to the birth canal, it may be entirely within the pelvis as a retroperitoneal hematoma or occasionally as an intraperitoneal hemorrhage.

The second obstetrical accident which may cause shock is rupture of the uterus and this is probably more common than is recognized clinically. It is most common through the scar of a previous section and next after difficult operative deliveries. However, it sometimes occurs spontaneously in unobstructed labors. Rupture of the uterus per se seldom produces clinical evidence of shock and when the latter develops it is secondary to hemorrhage.

Shock may be also due to inversion of the uterus. This may occur spontaneously or be due to unskillful management of the third stage of labor. A considerable number of these cases go into shock quickly. The remainder go into shock either as a result of hemorrhage or from attempts of replacement which are frequently accompanied by bleeding. All these cases should therefore be looked upon as potential cases of shock and prophylactic measures against this condition should be instituted at once before any attempt at its correction is carried out. Nevertheless all cases of inversion do not show shock. During the past 10 years

7 cases of acute inversion were seen by the author.   One had profuse bleeding with severe shock, 2 had moderate hemorrhage and moderate shock, the other 4 had no evidence of shock.

Shock is sometimes the cause of death in eclampsia and even in pre-eclampsia. A rapid delivery or deep anesthesia may aggravate a potential case of shock. The collapse that follows delivery in cases of hypertension is probably explained by sudden lowering of the intra-abdominal pressure with a filling of the splanchnic vessels with noncirculating blood.   When death does not result quickly from the shock it may occur later from damage to the central nervous system due to cerebral anemia.

In the management of obstetric shock prophylaxis is of great importance. If the obstetrician has constantly in mind those conditions leading to shock, most particularly hemorrhage, he will make every effort to obviate them and to provide for their treatment before constitutional symptoms have made their appearance. In the case of hemorrhage the blood loss should be replaced as rapidly as possible and the prevention of further bleeding carried out.   In cases of hypertension, delivery should be slow and after delivery if there is a marked drop in blood pressure, a tight abdominal binder should be applied.   Mechanical trauma should be kept at a minimum and when it occurs it should be recognized and treated.   In all cases of inversion of the uterus antishock therapy should be instituted whether shock is present or not.

Pain and apprehension should be abolished by the use of morphine.   Normal body temperature should be maintained by the usual methods.   Replacement of the circulating blood volume should be immediate, preferably with blood, and if no blood is available, plasma, and if no plasma is available, intravenous glucose.

When shock has appeared the trauma of any operative procedure should be avoided except where such procedure is necessary to stop active hemorrhage. In placenta previa measures to stop the hemorrhage should be carried out while the replacement of the lost blood is going on.   In cases of accidental hemorrhage where shock does not exist, conservative treatment is most apt to avoid the development of shock.   The author believes that there may be a place for cesarean section in the treatment of toxic accidental hemorrhage but believes the place is small.   Where severe shock does not exist and the baby is still alive and viable section may be indicated in the interest of the child, and in a few cases where fresh hemorrhage continues to occur and labor does not supervene, it may be indicated after the shock has been treated.

(As might be expected from Scott, this article is a well-rounded appraisal of obstetric shock and contains much sound advice.   It will be noted that 2 of the 6 deaths occurred in cases of placenta previa and the author goes on to say: "Both cases had immediate transfusion and were treated by version.   Both died following postpartum hemorrhage."   This drives home again the warning, already stressed in this issue of the Survey, p. 335, that in many cases of complete and partial placenta previa the cervix and lower segment are so friable as to make abdominal delivery the only safe procedure.

The author's statement that the place of cesarean section in abruptio is a small one recalls that there is still much difference of opinion about the best method of delivering these patients.   For my own part, I lean decidedly toward abdominal delivery in all clear-cut

examples of this disorder unless the patient is in labor, or the cervix very favorable for its initiation by rupturing the membranes. However, the maternal mortality in any given series of cases is likely to depend more on the promptness and liberality with which blood transfusions are given than on the method chosen for delivery.—Ed.)

INVERSION OF THE PUERPERAL UTERUS

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JOHN RANKIN

Coquille, Oregon

In 1939 the authors reported a case of spontaneous inversion of the uterus 5 days postpartum, following prolonged efforts to empty a distended bladder. A Spinelli operation was done and follow-up was satisfactory. A second case is now reported.

Past history of the 17-year-old primipara was irrelevant except for a reported fractured pelvis in an auto accident. Measurements and laboratory tests were normal, prenatal course, delivery and immediate postpartum period uneventful. There was a delay of 40 minutes in delivery of the placenta, but separation and expulsion were not considered unusual and no forceful Crede was used. Patient went home on the 6th day.

On the 13th postpartum day, while attempting to expel a difficult stool, she felt a mass suddenly protrude from the vagina. She was hospitalized at once and an effort was made to reduce the inversion manually. However, she went into shock with hemorrhage and additional efforts were delayed. Repeated transfusions of citrated blood were given. Involution of the uterus was awaited, and a Spinelli was performed 28 days later.

The technique of a Spinelli consists of incising the anterior wall of the inverted uterus from the level of the cervix to the fundus. The uterus is then restored by rolling the cut edges laterally while at the same time gently pressing the fundus up toward the pelvis. The normal relationships are readily obtained. A wedge-shaped piece is excised from each side of the incised uterus before the walls are sutured. The corpus uteri is replaced in the pelvis and the defect in the anterior fornix sutured. A vaginal pack of iodoform gauze is left in place for 24 hours and then cautiously removed.

If, after suturing the incised walls together, the uterus is too large to be replaced within the pelvis, one can excise more tissue from the lips of the incision or inject 1 cc. of pituitrin into the uterus. In this reported case, difficulty was still experienced. Eventually a small low midline abdominal incision was made and the

uterus easily pulled up by means of a ring forceps and a traction suture in the fundus. Penicillin was given postoperatively.

It is suggested that if one were to make an inverted T incision, such as commonly used in repair of a cystocele—if, in addition to the usual transverse incision across the anterior fornix above the cervix prior to incising the body of the uterus, one continues at right angles to the transverse incision up and out toward the urethra—there should be ample room through which to replace the uterus.

The reported incidence of inversion of the puerperal uterus ranges from 1 in 2000 to 1 in 210,000, mostly around 1 in 4000 to 1 in 8000. The mortality rate tends to be 30–40 per cent. Induced inversions constitute the majority of the cases, but incidence of spontaneous inversion may be 13–50 per cent.

A fundamental underlying cause of inversion is a relaxation of the upper fundal segment of the puerperal uterus. The relaxed fundus invaginates into the cavity of the puerperal uterus, acting as a foreign body which the uterus quickly tries to expel, resulting in inversion.

For immediate reinversion, before shock and hemorrhage have ensued, the patient is anesthetized and placed in lithotomy position. If there is already some contraction, it can be relaxed by 1 cc. of 1:1000 solution of epinephrin or 1/100 gr. of atropine given intramuscularly into the deltoid. By manual manipulation, beginning at the cervix and extending back and down to the fundus, the uterus is steadily massaged up through the cervical ring back into the pelvis. A tight vaginal pack of iodoform gauze is left in place 24–36 hours and then slowly removed. In the interval, plasma or whole blood transfusions are given with oxytocics sufficient to keep the uterus firmly contracted.

If shock and hemorrhage occur, these are treated first. When the patient's condition warrants and the uterus is well involuted, the uterus is reinverted by vaginal or abdominal surgery. These later cases are more commonly seen. The authors prefer a Spinelli operation, feeling that the abdominal method produces more shock and more danger from infection. Although they have not done the Haultain operation, in which the abdomen is opened as for a pelvic operation and inversion corrected by an assistant pressing on the fundus from below simultaneously with the operator retracting from above, they feel it offers more hazards than the Spinelli. It may be necessary in the Haultain also, more often than not, to incise the posterior lip of the cervix in order to replace the uterus. In both operations the cervix and/or body of the uterus is incised and in both infection may exist. The possibility of rupture of the uterus following a Spinelli is felt to be exaggerated.

Although some have performed hysterectomies following inversions, if shock and hemorrhage can be controlled, hysterectomies can be avoided.

(In Frederick C. Irving's exhaustive consideration of inversion of the uterus, published as Chapter 92 in Curtis' Obstetrics and Gynecology (Vol. 3, pp. 641–659, W. B. Saunders, 1934), he quotes an analysis by Thorn of 641 cases from the literature as follows: "He (Thorn) found 19 occurring directly after the birth of the child, 44 after the delivery of the placenta, 141 within 12 hours postpartum, 67 within 6 weeks, 52 within 12 months and 40 after 1 year." Thorn's review, "Zur Inversio uteri," was published in Leipzig in 1911. If

we may judge from these figures it is clear that such cases as McKeown and Rankin report, although extremely rare, are not unknown. In the opinion of McCullough (J. Obst. & Gynaec. Brit. Emp. *32:* 280, 1925) these supposedly late inversions represent cases in which an incomplete inversion occurred actually in the third stage but was not recognized until some days or weeks later when an episode of coughing, vomiting or straining converted it into a complete inversion. This explanation would seem more credible than the assumption that a well involuted uterus, with no tumor in it, could invert so long after delivery.

In regard to McKeown and Rankin's statement that "The possibility of rupture of the uterus following a Spinelli is felt to be exaggerated," it is well to recall that Onslow Gordon (Am. J. Obst. & Gynec., *32:* 399, 1936) reported a case in which a woman died, following an easy labor, 2 years after a Spinelli operation. The cause of her death was rupture of the uterus, the rupture having taken place through the scar of the Spinelli operation.—Ed.)

ABDOMINAL PREGNANCY: BIRTH BY RECTUM

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This is an unusual history of a 25 year old colored para 0 who was first seen in the emergency room of the Parkland Hospital in Dallas, Texas, on January 5, 1946, with a complaint of vaginal bleeding and cramping lower abdominal pain. Her last menstrual period was August, 1945. Since November 15, 1945 there was intermittent vaginal spotting. In early December an episode of severe para-umbilical cramping pain and dysuria occurred. Examination revealed a moderate amount of vaginal bleeding and a softened cervix adjacent to a nontender cul-de-sac mass about the size of a 2 months' pregnancy. The uterine body was not outlined separately. A diagnosis of threatened abortion was made and the patient sent home with sedatives and directions to rest in bed. She again returned to the emergency room one week later with the same complaints of lower abdominal cramps, vaginal spotting and dysuria. She was thought to have pelvic inflammatory disease at this time and a Friedman test was obtained and reported as postive. About March 2nd the patient was admitted to the hospital. On examination an x-ray led to the diagnosis of secondary abdominal pregnancy. Since the fetal heart tones were audible and of good quality, it was decided to allow the pregnancy to proceed and the patient was released from the hospital after the 12th day.

The second hospital admission occurred on March 18, 1946, when the patient was readmitted weak, nauseated and toxic, complaining of chills, fever, pain in the lower abdomen, burning on urination, vaginal spotting and the absence of fetal movements for three days. Her febrile course improved for about 7 days but again relapsed and lasted 43 days. This produced a marked weight loss and nearly cost the patient's life. About the 25th day of the second admission she

began to pass blood per rectum and examination revealed a defect in the anterior rectal wall at the extreme reach of the index finger. The fingertip entering the hole encountered sharp bony structure. Her condition remained critical during the ensuing 33 days and on the 63rd day the fever began to subside, improvement occurred and the patient was discharged from the hospital on the 73rd day of the second admission, still retaining the fetal skeleton, some bones of which presented at the defect in the anterior rectal wall.

During the ensuing 4 months she passed by rectum fetal bones which she dutifully saved and brought to the clinic. All save the last and largest piece, a parietal bone bigger than a silver dollar, were passed with a minimum of discomfort. Following passage of the parietal bone the hole in the rectum began to close. When the patient was seen on September 20th, the defect in the anterior rectal wall would admit only the tip of the index finger. No other fetal bones could be palpated but induration still persisted in the surrounding pelvic fascia. Her menstrual periods had not recurred but in all other respects she had returned to normal.

In commenting upon this case the course of events within the abdomen was easily reconstructed. Pregnancy began with tubal implantation some time after August, 1945, the date of the last menstrual period. Tubal abortion with minimal internal bleeding and secondary placental implantation occurred before the appearance of vaginal spotting November 15, 1945. The pregnancy prospered for a time but succumbed March 15th from lack of blood supply or trophoblastic invasion of the large bowel or both. Contamination of the amniotic sac and peritonitis from bacteria present in the large bowel promptly ensued. After the onset of the peritonitis laparotomy was contraindicated with this patient. During the entire 43 day febrile period the amniotic sac was grossly infected since it formed a communicating diverticulum with the rectum. Formation of a rectal amniotic fistula was recognized clinically with the passage of blood from the bowel and confirmed by palpation of the defect in the anterior rectal wall.

The points of interest presented by this patient included: (1) The length of time between development of the recto-amniotic fistula and passage of the first fetal bones (nearly 2 months). (2) The onset of recovery despite the presence of the fistula. (3) Spontaneous closure of the fistula after the amniotic content was discharged; and (4) The complete healing of the internal genitalia without obvious residual scarring.

SPONTANEOUS DELIVERY OF PLACENTA IN FRONT OF FOETUS WITHOUT HAEMORRHAGE·

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This is the case of a 43 year old para 6 with 4 living children, who was admitted to the hospital on May 24, 1947 because of a prolapsed cord. Her last menstrual period was September 12, 1946, making her 37 weeks pregnant. Her course during pregnancy was thought to be normal.

At 5:30 P.M. on the evening of admission, spontaneous rupture of the membranes occurred with the escape of a moderate amount of blood stained amniotic fluid, following which the cord appeared at the vulva.

The patient was admitted to the hospital at 9:45 P.M. in good condition. Temperature was 98.2, pulse 100, blood pressure 134/88. Urinalysis was negative. Abdominal examination showed the fetus to be lying obliquely with the head in the right iliac fossa. Contractions were occurring every 3 minutes. The fetus was estimated to be small and no fetal heart could be heard. A protruding loop of umbilical cord could be seen on inspection of the vulva.

The patient was anesthetized, cleaned and a hand was inserted into the vagina. The placenta was encountered lying free but without any membrane attached. This was removed. The cervix was found to be dilated about 3–4 finger breadths, soft and thin. The presentation was a shoulder with the back anterior.

Internal version was then done with perforation of the aftercoming head. The retained membrane was then removed with forceps. The blood loss was not unusual. The cervix and lower uterine segment were carefully examined and found to be undamaged. The patient was given penicillin and the puerperium was entirely afebrile. The infant weighed 3 pounds and showed a marked degree of hypospadias and double harelip. There was no evidence of maceration. The placenta showed no gross abnormality and weighed 310 grams.

It is suggested that the possible mechanism was that the placenta had a poor attachment, becoming detached with the onset of pains and that the uterine contractions, possibly assisted by a mild degree of hydramnios, drove the presenting part down and plugged the placental area. If this was partly or largely on the anterior surface of the lower segment, the fetal back was ideally placed for the purpose. The assumption that the placenta was attached to the lower segment seems to be the only possible explanation that covers the 3 facts of primary placental separation, retention of membranes completely and absence of hemorrhage.

SOCIAL AND LEGAL ASPECTS

THE ABORTION PROBLEM IN SWEDEN

GUNNAR INGHE

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In Sweden attempts have been made to bring abortions under social control to reduce their frequency, and investigations have added to knowledge of the medical and sociological aspects of the problem.

Illegal abortions in Sweden have been estimated as at least 10,000 annually, and probably considerably more, among 130,000 total annual births. The mortality rate is probably below 0.75 per cent, but the incidence of postabortal infection is very high. Folke Holtz showed some years ago that a high percentage of sterility, perhaps 20–25 per cent, can be traced to illegal abortion. No increased risks have been found with later deliveries, however. Psychic disturbances, unless abortion is followed by sterility, have probably been highly exaggerated.

Among married women the frequency of illegal abortion is highest in the older age group, and among unmarried women in the younger. In the towns it is especially women from rural areas who are apt to seek abortions—characteristically, those in town only a few years, perhaps due to lack of knowledge of contraceptive methods. Relative abortion frequency is 6–10 times as high among the unmarried as among the married, although the actual number of abortions is quite as high among the married. Highest rates are found among employed women—waitresses, hairdressers, shop girls—and where there are economic factors such as poverty, crowded quarters, and large families.

Social and economic difficulties are found to play the greatest role. For unmarried women especially, the difficulty of continuing with employment or training is important. Medical and eugenic motives are sometimes given, but the diseases involved are usually minor. Personal motives are also important. Some women regard themselves as too old or too young for children; others are unwilling to change their scheme of life and encounter the new factors. For unmarried women the conventional motives are the most important, including sensitivity to public opinion, fear of the parents' reactions (especially among the younger women this motive is strong and may even lead to suicide), and the reaction of the man.

As a rule illegal abortions in Sweden are performed by charlatans, sometimes by relatives or friends, very rarely by physicians. All kinds of people are included, skilled and unskilled, profiteers and ideally disposed persons, former prison inmates, psychotics. A great many women induce an abortion upon

themselves; a record of some of the details will be found in the report of the Population Investigation Committee.

The woman who desires an abortion finds herself isolated with her problems and difficulties. The primary task of the community should be to try to break through this isolation and establish contact with the woman in order to prevent the desire for abortion from being carried into action.

Attempts have been made to attain this through the appointment of special curators, associated with the Institution for the Protection of Motherhood, for women who seek abortions. Ten bureaus will be established under government subsidy in connection with the polyclinics of the hospitals, with a physician and a woman curator in each. All abortion applicants will thus have an opportunity to approach or be referred to a curator. Personal support and encouragement, aid in conflicts with parents and partners, and information about the risks involved will be provided. In this way it may be possible to avert an abortion. The curators have also authority to give a certain amount of actual economic assistance in order to provide immediate relief. They should also have facilities for placing these women to get any extra social assistance required. A new law is being considered to prohibit the dismissal of employed women because of pregnancy. Increased maternity economical assistance has also been proposed to enable working women to remain at home during the 6-month rest allowed by law. Added experience will indicate other possible measures.

The first step, however, is to establish contact. Toward this purpose, it has been made possible for women to obtain physical examinations and urine tests for pregnancy free of charge at all maternity centers. Also, abortion is now legally permitted under certain special circumstances. To induce women to call on the curators for assistance, which in many cases brings a change of mind, it was necessary for the curator to be in a position to act as advisor in the matter of the decision on the abortion. Only by offering a hope of having the operation performed is the prospect possible of establishing contact with all the women who are distressed by pregnancy.

Since 1939 abortions have been allowed by law on medical indications as well as on humanitarian and legal grounds. The term "general weakness" was used as a medical-social indication for abortion, applied primarily to women weakened by repeated child-bearing, but was rarely put into practice. In 1945 the Riksdag widened the indications for abortion, permitting abortions in cases where "considering the social condition and other circumstances of a woman, her health might be harmed by the birth of the child and its care," and pointing out that the social factors should receive greater emphasis. This was a necessary factor in the abortion-prophylactic program, should lead to a considerable reduction in the number of illegal abortions, and should enable the curators to intervene in many cases at the psychologically critical moment. The Medical Board has been authorized to sanction or refuse a legal abortion on this wider basis; 2 consulting physicians can still sanction an abortion on their own initiative.

There is now exemption from penalty for submitting herself for illegal abortion for the woman where extenuating circumstances exist, although punishment has not been entirely repealed.

Another phase of the abortion-prophylaxis program is the intensification of sex education. An educational program against abortion has been started, and sex education will be introduced in the schools. Free consultations about contraception are provided at the Maternity Health Centers and the chemists are obliged to supply preventives at reasonable prices.

These different lines of action constitute a continuous program which should probably lead to a substantial decrease in the number of illegal abortions. The program is experimental, and changes are both anticipated and desired.

The greatest difficulty will be in the general attitude toward unmarried mothers. Many legislative reforms are required, and a more positive and understanding attitude must be adopted toward motherhood in general.

The author feels that the penalty for submitting to illegal abortion is a very minor restraining factor. The primary factors with a restraining effect are the fear of physical risk and an aversion toward the destruction of the fetus (a maternal feeling which usually develops after the first couple of months, if enough time can be gained). The penalty is in some respects an obstacle and should probably be revoked—many women dare not approach the social institutions for fear of retaliation in case an illegal abortion is later performed, and tracing of professional abortionists is made more difficult.

It has been suggested that indications for legal abortions be extended even further. At present the best policy is probably a waiting attitude until the results of the new abortion-prophylaxis program become established.

MISCELLANEOUS

OBSTETRIC AND GYNECOLOGIC MORTALITY AT PARKLAND HOSPITAL 1944, 1945 AND 1946

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All deaths occurring on the obstetric and gynecologic service of Parkland Hospital during 1944, 1945 and 1946, were reviewed by the Department staff to decide cause and assign preventability and responsibility. During these 3 years 7214 patients were admitted and 55 died. Seventeen of the deaths were on the obstetric service and there were 38 gynecologic deaths.

In a breakdown of these figures it was found that the leading cause of death was malignant neoplasm. There were 21 deaths due to cancer and other malignant tumors. Thirteen of these died of carcinoma of the cervix, 2 of carcinoma of the ovary, 1 of sarcoma of the mesentery and 5 unknown.

The next cause of death was abortion. There were 6 fatalities due to incomplete abortions and 2 of the 6 were associated with multiple perforations of the uterus. One resulted from a bacillus Welchi infection. All patients in this group were treated conservatively. Except in the event of life-endangering hemorrhage infection was controlled before performance of a dilatation and curettage. The mortality rate was 1.2 per cent and no deaths occurred from hemorrhage.

There were 3 deaths during this period due to hysterectomy. Two hundred and thirty-four hysterectomies were performed during this time and usually were of the total variety. There was 1 obstetrical death due to hysterectomy. This was performed when the patient was moribund (uterine rupture) in a desperate and unsuccessful attempt to save her life. The second death due to a subtotal hysterectomy was ascribed to anesthesia. The totally hysterectomized patient died of peritonitis.

There were 4 deaths among 879 other gynecologic operations. By adding these to the hysterectomy statistics there were 7 deaths among 1113 operations, a rate of 0.63 per cent. The first fatality was considered an anesthetic death. In the second it was believed that the operation activated a latent amebic infestation. In the third case hemorrhage and shock produced death and the fourth was due to shock following bilateral hypogastric ligation to check hemorrhage from advanced cervical carcinoma.

Of the incidental causes of gynecologic mortality 1 patient with a huge myoma and hypertension died of myocardial failure. Another died of anuria following a blood transfusion and another died of peritonitis, cause undetermined.

The sole fatality due to extrauterine pregnancy involved a patient dying with massive internal hemorrhage 20 minutes after entering the hospital. This 1 death occurred among 36 extrauterine pregnancies, a rate of 2.8 per cent.

In analyzing the obstetric deaths, 17 in number, it is seen that during 1944, 1945 and 1946, 5025 patients were admitted to maternity, and 4123 women or 82.2 per cent were delivered of infants weighing 1500 or more grams. Seventeen of these women died, a rate of 4.1 per 1000 births.

A little more than $\frac{1}{4}$ of the delivered women were first seen in labor, usually as obstetric emergencies. Of this group 1135 women receiving either no prenatal care or inadequate care elsewhere, 14 died, a rate of 12.3 per 1000. There were only 3 deaths among a group of 2988 women attending Parkland Prenatal Clinic 1 or more times, a rate of 1.0 per 1000. This is a considerable contrast and shows the efficacy of prenatal care.

Six patients died of toxemia of pregnancy, 3 with convulsions and 3 with non-convulsive toxemia. During this 3-year period 358 patients, 21 with convulsive and 337 with nonconvulsive toxemia, were admitted to the hospital

Five of these deaths were concentrated in an 8-months period during 1945. At the time the service was new and departmental philosophy was developing. It is believed that as a result of the desire to "do something" these 5 patients dying during this period were overloaded with fluid. All save 1 developed pulmonary edema and cerebral edema was seen at the postmortem examination in that patient. Two patients received quantities of sedative drug approaching the minimal lethal dose. It is evident that death from toxemia of pregnancy is usually preventable and that overtreatment represents a potent threat to the life of the toxemic patient. The authors believe that effective treatment is limited and includes absolute bed rest, sedation, restriction of the sodium ion in edematous patients only, and interruption of pregnancy. If this regime is carried out in all but the mildly ill, everything possible has been done for the patient. From this point on the authors believe that treatment tends to become meddlesome.

There were 4 deaths from puerperal infection, a rate of 0.97 per 1000 births. One patient died on the 14th day with puerperal peritonitis, another on the 7th day with symptoms of embolism. The third patient died on the 29th day with massive pulmonary embolus. The fourth succumbed on the 12th postoperative day following a Waters' extraperitoneal cesarean section for cephalopelvic disproportion. This death was ascribed to an error in judgment since either craniotomy or cesarean hysterectomy would have been preferable to extraperitoneal section in the presence of infection.

Five patients with uterine rupture were observed during the 3 year period. The first died 54 minutes after delivery due to an extension of an old repaired cervical tear immediately after spontaneous expulsion of a normal baby. The second death, due to rupture of the uterus, followed manual removal of the placenta, the patient dying after hysterectomy. In the third case the etiological factor was pituitrin administered during labor and prior to admission. This patient died after hysterectomy. The fourth case was one of neglected transverse presentation with a prolapsed arm. This patient likewise died after

hysterectomy. The fifth case was one of spontaneous rupture of the uterus in a secundigravida admitted in early labor. There was no dystocia, no oxytocic and no interference of any kind. No explanation for this rupture of the uterus can be given. The patient died following hysterectomy. All 5 ruptures were primary but none followed previous cesarean section. Rupture of the uterus occurs much more often than is diagnosed or even suspected. It must always be considered when the blood pressure drops unexpectedly during or immediately after delivery.

There was 1 death due to puerperal hemorrhage. This was a private patient who was allowed to enter labor with a hemoglobin of 5 grams. A stillborn infant followed midforceps operation. Two minutes later the placenta was removed manually; uterine atony ensued following which vaginal bleeding and shock occurred. During the ensuing $1\frac{1}{2}$ hours 1200 cc. of blood were lost. The patient was then transfused with blood and plasma. However, she died 2 hours and 20 minutes after delivery.

In the incidental causes of death 2 patients died with pulmonary tuberculosis. Another patient succumbed with septicemia following a scratch on her hand and a patient with a low hemoglobin following birth of a hydatidiform mole, developed nephrosis with complete anuria following a blood transfusion.

The stillborn and neonatal mortality rate for term sized infants, 2500 grams or more, was 21 per 1000. Eleven and three tenths per cent of all newborn infants were all immature (1500 to 2400 grams). There is no obvious explanation for this very high incidence of immaturity. There was a great loss of life among the prematurely born infants (38 per cent) and more than $\frac{3}{4}$ of them died neonatally. The overall stillbirth and neonatal death rate for potentially viable children (1500 grams +) was 62.1 per 1000 births.

Maternal Mortality Reports

(Secretaries of Maternal Mortality Committees are invited to submit selected cases of maternal deaths, with analyses appended, for publication in this section of the Survey. Cases should be chosen on the basis of educational value, not because of rarity. For obvious reasons complete anonymity will be maintained.

Readers should note that the comment which follows each case history represents the opinion of the Committee concerned and does not necessarily reflect the attitude of the Editors.)

TWO OBSTETRIC DEATHS ASSOCIATED WITH CYCLOPROPANE AND PITUITARY EXTRACT

Reprinted from the News Letter of the American Society of Anesthesiologists, Inc.

(Courtesy of Dr. HAROLD F. BISHOP, Editor, Case Reports)

CASE REPORT NO. *42* (VOL. 9, NO. 4, 19–21, APRIL, 1947)

The patient was a 24 year old primigravida admitted to the hospital on January 25, 1947 with abdominal pains every 10 minutes, slight bloody show and intact membranes.

The patient's prenatal course was entirely normal; there was no evidence of any toxemia of any kind, the blood pressure was perfectly normal throughout her prenatal course.

On admission the patient's temperature, pulse and respiration were all normal, and the blood pressure was 118/70. Initial rectal examination showed the vertex to be dipping into the brim, the cervix partially effaced and open 2 cm. The patient had a perfectly uneventful 1st stage of labor which lasted 12 hours. After a 1 hour and 2 minute second stage, the patient delivered a living female child by low forceps extraction weighing 6 lbs. and 11 oz. A left mediolateral perineotomy was performed and there was no extension. The delivery was executed under cyclopropane anesthesia. During the anesthetic the patient had a short period of apnea; the respirations returned spontaneously, the pulse remained normal throughout. The cyclopropane was administered for 20 minutes. The 3rd stage was 3 minutes in duration and normal. The patient received 1 cc. of pituitrin intramuscularly after this 2nd stage. There was no excessive bleeding at any time during the 2nd and 3rd stages of labor.

Following the 3rd stage of labor, the patient was undraped but left on the delivery room table as is the custom. At that time the anesthetist declared that the patient's reflexes had returned. The patient was breathing normally, condition was good, pulse was normal, the fundus was firm and there was no excessive bleeding. Fifteen minutes later the patient had ceased breathing. There was no heart beat evident, and the patient's color was one of dusky gray color, not one of deep cyanosis. After it was ascertained that there was no respiratory obstruction, oxygen was given with positive pressure, 1 cc. of adrenalin given intracardiac as was 5 cc. of coramine, all with no effects. The patient was pronounced dead at 8:45 a.m. on January 26, 1947.

There was no evidence that the patient had had any convulsions or twitchings while on the table. There was no deep cyanosis that is associated with a respiratory failure type of death. Fundus was firm, and there was no evidence of any bleeding either abdominally or vaginally. There was no evidence during the prenatal course that the patient had any heart disease. Physical examination on admission into the hospital, as was the history, was entirely normal. No postmortem examination was obtained.

Cause of death is not determined. Medical Examiner declared this an anesthetic death and indicated that a postmortem was not necessary.

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Comment on Case No. 42 by W. W., New York. In discussing Case Report No. 42, there is very little in the history that would point exclusively to any one mechanism being the cause of death.

The prenatal course was apparently normal. The patient's cardiac condition must have been good since she stood a 13 hour labor without showing any signs of cardiac distress; and the labor and delivery were apparently not remarkable except that the patient had a short period of apnea. Why this should be is not clear, and I have not known of any reports that cyclopropane depresses the respiratory center.

Patients have been known to react badly to pituitrin. I have seen some get extremely pale, the pulse volume markedly reduced so that the radial pulse is almost imperceptible, the effect apparently being on the cardiac muscle, particularly if the intramuscular injection was by accident given intravenously. Its use intravenously, while in vogue for several years, has been gradually given up. The only argument against this point of view as being contributory to the death is the fact that after the anesthetic the patient was declared by the anesthetist to have a good pulse and to have a complete return of her reflexes. However, the reaction could be delayed.

I see no other reason why a perfectly normal healthy young primigravida, delivered so normally, should succumb in so sudden a manner.

"But see Dr. Bishop's comment following Case Report No. 54."

CASE REPORT NO. 54 (VOL. 11, NO. 12, 16–18, DECEMBER, 1947)

This 28 year old gravida I, para O, was admitted to the hospital in mild labor at 3:30 a.m. on December 26, 1946 with history of onset of uterine contractions about 3 hours prior to admission.

Her past medical history was entirely irrelevant. The first trimester of pregnancy was uneventful except for some nausea and vomiting. During the second trimester, patient complained of intermittent episodes of weakness and syncope, even at bed rest. The course of the 3rd trimester was not unusual except during the last week urinalysis revealed few pus cells and 1 plus albumin. X-rays of chest and heart, E.C.G., and blood pressure were within normal limits. Weight gain during pregnancy was 19 pounds.

Immediately after admission, the patient was given luminal gr. III and received routine preparation including enema. By this time she was complaining of severe pain with her contractions and was given morphine sulfate gr. 1/4 and scopolamine gr. 1/150 at 4:25 a.m. At 8:00 a.m., the patient received nembutal gr. ISS and scopolamine gr. 1/150. At 12:30 p.m., membranes ruptured spontaneously. At 1:20 p.m., patient received morphine sulfate gr. 1/8 and prostigmine gr. 1/150 and at 5:45 p.m., seconal gr. III and scopolamine gr. 1/150.

This patient's labor was uneventful except for periods of extreme restlessness and irritability and one of the nurses on duty stated the patient had a mild convulsion, chewing tongue, about 30 minutes after the last sedation was given. About 7:30 p.m., the patient became quite restless and was taken to the delivery room where cyclopropane and oxygen were administered. At 8:35 p.m., she delivered a normal male infant with the aid of low forceps and routine episiotomy. Blood loss was only slight and the patient received the routine intravenous ergotrate and intramuscular pituitrin.

As the patient reacted from the anesthetic, she became violent requiring morphine sulfate gr. 1/4 at 9:20 p.m. Blood pressure was 110/70 and pulse rate was 90. About 10 minutes later the patient became cyanotic and expectorated bloody frothy sputum. Oxygen, caffein-sodium benzoate were administered without response and the patient expired a few minutes later. Intubation was done.

An autopsy was performed revealing nothing of significance except massive pulmonary edema and congestion of unknown etiology, acute pyelitis and a moderately advanced hydronephrosis.

Comment on Case No. 54 by W. E. S., New York. I have reviewed this case and find that essentially it consists of a primiparous patient who was in labor for about 17 hours and who received during her labor a total of $\frac{1}{50}$ gr. of scopolamine, $\frac{5}{8}$ gr. of morphine and $7\frac{1}{2}$ gr. of barbiturates, fairly widely distributed over the entire course. The sudden death took place after cyanosis and dyspnea shortly after delivery.

I would suspect that this was on the high side as far as the administration of such drugs were concerned but believe I have seen many patients receive thus much during a labor of this duration without observing the after effects which followed in this particular patient. I suppose that one of the explanations of her sudden pulmonary edema would be sudden maternal anoxia produced by barbiturates, morphine and scopolamine. There is no mention as to the fetal result in this case, whether the infant was born alive or dead. I believe that if this infant showed minimum signs of drug overdosage it would not seem likely to me that the mother's death could be explained on the basis of over-sedation. Her sudden death occurring shortly after delivery with cyanosis, might be explained on the occurrence of a diffuse embolization and pulmonary arterioles by the particulate matter in amniotic fluid.

Eight such cases were described in 1941 by Steiner and Lushbauger. You will find a report in the J. A. M. A., Volume 117, pages 1245 and 1340. I would think it might be of extreme importance in this case to review the sections of the mother's lungs to determine whether this lesion might be present. It has frequently been overlooked in patients who died suddenly during labor or after delivery.

Comment on Case No. 54 by H. F. Bishop. In its essential details, the course of the patient in Case Report 54 was the same as that of the patient in Case Report 42, published in the April, 1947 issue of the News Letter. In my opinion, the deaths of both these patients are ascribable to the totally unwarranted use of pituitrin for a patient under cyclopropane anesthesia. It is my further opinion that the explanation offered by W. E. S. is totally unsatisfactory and unlikely.

By referring to any modern, standard textbook on pharmacology, one is able to learn certain facts which are both pertinent and highly significant to such cases as these. For instance, concerning pituitary extract, it is well established that its administration leads to (a) constriction of systemic arterioles and capillaries, (b) even more marked constriction of the coronary and pulmonary arterioles, (c) slowing of the heart, (d) dilatation of the heart and weakening of its beat, (e) reduced cardiac output and fall in pulmonary arterial pressure as results of (b) and (d).

Concerning cyclopropane it is (or should be) well known that this agent, like chloroform, renders the hearts of experimental animals highly susceptible to the development of ventricular fibrillation, so that they are, as it were, sensitized and ready to fibrillate upon the least provocation. It is also known that spontaneous

fibrillation under cyclopropane is most likely to occur when the subject is passing from a deeper to a lighter stage of anesthesia. This is undoubtedly related to the increased output of adrenalin which occurs as the patient recovers consciousness. As long as it is the "routine" to administer pituitrin to obstetric patients who are under cyclopropane anesthesia, so long will such deaths as these be occurring with distressing frequency. They will almost without exception occur in the manner described in both of these case reports; that is, they will occur with absolute abruptness and finality just as the patient is "reacting" from the effects of the cyclopropane anesthesia. At this stage, the effects of the pituitrin are usually attaining their maximum (the maximum effects being attained about 20 minutes following intramuscular injection); at this stage, also the myocardial irritability induced by the cyclopropane is maximal, as is also the additional detriment imposed by the patient's own adrenalin-production. The simultaneous occurrence of these 3 *noxae* will inevitably lead to a fatal termination in some of the cases.

There have been, in this community during the past year, 2 deaths of women in delivery rooms which followed the identical pattern described in these 2 case reports. Each patient received the "routine" dosage of pituitary extract while under cyclopropane, and each died abruptly just after regaining consciousness. It is my conviction that it is part of my duty and responsibility as an anesthetist to see to it that no patient is given pituitrin while she is receiving cyclopropane.

Thus, in offering my answers to the specific queries which you made concerning the patient of Case Report No. 54, I would say:

1. This was a preventable death from the standpoint of anesthesia.

2. No, it is not fair to ascribe the death to the "agent or method" primarily.

3. In that the anesthetist not only did nothing to prevent the use of pituitrin, but actually accepted it as merely a "routine" procedure, it was preventable due to the improper management of the anesthesia period.

4. It was not due to improper resuscitation for these deaths are absolutely final, and the likelihood of resuscitating such a patient is *nil*.

MATERNAL MORTALITY IN SCOTLAND, 1911-1945

Extracted from the 91st Annual Report of the Registrar General for Scotland

By P. L. McKINLAY

Medical Superintendent of Statistics
Edinburgh, His Majesty's Stationery Office, 1947

AN ABSTRACT OF DR. McKINLAY'S REPORT

Maternal mortality in Scotland, which was slowly but steadily increasing from 1911-30, fell suddenly and appreciably in 1931, where it remained virtually stationary until 1935. Then it dropped in 1936-7, again very substantially,

with improvement subsequently until 1941 but at a slightly retarded rate. From 1941 improvement again set in at a rate even greater than from 1935–41. The pre-1930 increase was almost wholly in the rate from sepsis; the sudden fall in 1931 was confined to the non-septic rate; the improvement from 1935–41 was again almost solely in puerperal sepsis; but since 1941 both broad groups have shown remarkable and persistent decline.

The numerically most important cause of maternal death apart from sepsis is *eclampsia*. Mortality from this cause has shown quite wide annual variations, but its general trend, until recent years at least, has been decidedly disappointing. Apart from a fall in mortality in 1914–16 there is a suggestion in the rates of a slight increase up to 1930, subsequent to which and for the next 10 years the trend was slightly downwards, the quinquennial rates in 1926–30 and 1936–40 being 114 and 95 per 100,000 live births respectively. The last 5 years of the series, however, have witnessed a quite striking and reassuring change, the rates in the last 2 years of the series being the lowest attained so far. The average for 1944–5 is only 57, or half the value registered in the quinquennium 1926–30. The long-continued downward course of the birth-rate with consequent increased primiparity may, in this cause particularly, have obscured an improvement of greater degree when the whole period under review is considered, and it is noteworthy that the greater rate of improvement in the last 3 or 4 years has taken place in spite of some intensification of the adverse change in the general parity constitution of pregnant women.

Puerperal hemorrhage is the next main cause, in order of numerical importance. Unfortunately, this is a heterogeneous group not separately shown in our statistics prior to 1931. In this group (as constituted prior to 1931) can be recorded a general improvement over the 35 years under review, the rate of 83 in 1911–15 having been steadily reduced to 61 in 1936–40 and to 50 in 1941–5. The rate of improvement was fairly constant during the first 20 years to 1930, but since 1931 has appreciably speeded up.

Abortion: Up until 1930 the figures for this cause showed no evidence of improvement but rather the reverse, although the increase actually observed is of doubtful significance. There was a major interruption of trend in 1918 and to a less extent in 1919, when the rates shot up from an average in 1911–15 of 37 to 103 and 62 per 100,000 respectively. This undoubtedly was directly associated with the influenza pandemic of the same years. In 1931–35 the general level of the rates was higher than in 1911–20 and the annual fluctuations were of greater magnitude; but since then there has been a slight tendency towards reversal of the previously unsatisfactory trend, although the extent of improvement during these last 15 years is small. The quinquennial rates were 52, 50 and 45 in 1931–5, 1936–40 and 1941–5 respectively. Septic and non-septic abortions were not separately distinguished prior to 1931, and these more recent figures are dealt with later.

Phlegmasia alba dolens, embolism: The quinquennial values for this group are practically level, and there are no striking features to be elicited from scrutiny of the annual figures.

Uncontrollable vomiting: This cause has shown relatively wide changes of mortality rates throughout the period. The rates were rather lower in the latter than in the first half of the decennium 1911–20, but from 1921–5 there was a steady and rapid increase to values which in 1926–30 were precisely double those prevailing in the first decennial period. Subsequent to 1926–30 the rates fell irregularly in the next 10 years but only to values still well above those of 1911–20. Since 1940, however, a phenomenal decline has set in and for the last 3 years of the series the rates are virtually negligible.

. Comparing 1936–40 with 1931–5 the only significant changes in evidence are the decreases shown in respect of puerperal sepsis, placenta previa, "other" accidents of pregnancy, "other" and unspecified conditions and puerperal albuminuria and convulsions, which are respectively 56, 67, 46, 54 and 89 per cent of their earlier values. The decline in sepsis to 56 per cent of the 1931–5 rate contrasts markedly with that for other causes as a whole, namely 91 per cent. In 1941–5, a much more extensive change occurs. The general maternal death-rate has now fallen to 60 per cent of the 1931–5 level, sepsis to 33 per cent and other causes to 75 per cent.

In 1936–40 there were 2,119 maternal deaths, 571 fewer than would have occurred had the rates of 1931–5 been operative. Of these 571, no fewer than 419 are attributable to the improvment in puerperal sepsis alone. In 1941–5 there were 1,696 maternal deaths, a saving of 1,113 on the 1931–5 standards. Of these, 663 are attributable to the decline in puerperal sepsis, 111 to albuminuria and convulsions, 95 to uncontrollable vomiting, 81 to placenta previa and 47 to accidental hemorrhage. Thus in 1936–40, 70 per cent of the saving of life is in sepsis and even in 1941–5, with the rapid improvement in other conditions, appreciably more than half is in sepsis.

From the present review it would appear that in this group of maternal deaths only minor changes took place before 1931. The sudden change observed in that year has no relevance to actual improvement in childbearing risks and seems almost certainly due to altered office procedure. The first event of major importance was the sudden and steep decline in puerperal sepsis starting about the year 1936 and, with minor interruption, continuing until the present day, and this occurred at the same time and approximately to the same degree in all area aggregates of the country. Correlated with the discovery of new methods of therapy of easy application it seems likely that the relationship here is one of cause and effect. That this is not the sole explanation, however, is indicated by the fact that there occurred a similar trend of incidence which seemed to precede, in point of time, the decline in mortality, and suggestive of the intervention of a factor or of factors of preventive import. This may be related to the expansion of knowledge of methods of transmission of the infective agent which became available around the year 1930.

Prior to 1941 little striking change was manifest in causes other than sepsis, but puerperal hemorrhage did show a small degree of improvement, accelerated after 1931, over the whole period reviewed, and eclampsia showed slight decline during the years from 1930. Since 1941 more elaborate improvement has been

in evidence, relatively greatest in hyperemesis gravidarum, eclampsia, placenta previa, accidental hemorrhage and ectopic pregnancy.   The saving of life in the last 10 yars, even in the last 5 years, by the diminution of puerperal sepsis mortality, however, outweighs the collective improvement attributable to these other causes of death.

Quinquennial Rates fof Maternal Mortality in Scotland, 1931–45

Per 100,000 Live Births by Causes of Death

(From McKinlay,—but order in which causes of death are listed has been changed in order to group together the various septic, toxemic and hemorrhagic causes.)

	RATE PER 100,000		
	1931–5	1936–40	1941–5
Puerperal sepsis	215	120	71
Post abortive sepsis	37	34	33
Phlegmasia alba dolens, embolism	36	38	34
Albuminuria and convulsions	85	76	61
Uncontrollable vomiting	27	23	7
Other toxemias of pregnancy	21	19	15
Placenta previa	29	20	12
Accidental hemorrhage	24	21	14
Other puerperal hemorrhage.	40	41	39
Abortion, nonseptic	14	16	12
Ectopic pregnancy	13	10	6
Other accidents of pregnancy	6	3	5
Other accidents of childbirth	54	57	57
Other and unspecified conditions	11	6	7
All causes	613	483	377
All causes less sepsis (+ postabortive sepsis)	361	329	274

Gynecology

MALE HORMONE IN GYNAECOLOGY AND OBSTETRICS AND IN CANCER OF THE FEMALE BREAST*

By ALFRED A. LOESER, M.D.

London, England

PART 1

Introduction

In 1937 the author of this review, and at about the same time a number of French gynecologists, (1, 2, 3) attempted to introduce the use of the male sex hormone into gynecological therapy, having previously demonstrated its chief effects on the human endometrium and the anterior pituitary (4). A decade

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*The Collective Reviews published in the Survey represent the views of those invited to present them, and not necessarily those of the Editors.

of clinical experience with testosterone in gynecology, with reports from many authors throughout the world, has elapsed since then.

But when the writer reported his results to the International Congress of Gynaecology at Amsterdam (5) in May, 1938, with the encouragement of the late Professor Laqueur, who was the first to isolate testosterone (1935), no one seemed inclined to inject male hormone into the female body.

Even today many gynaecologists, for instance Hamblen, refuse to use the male hormone in gynaecology, although in the beginning of his own investigations in 1937 (6), Hamblen thought it could be useful in menstrual disorders.

Is the male hormone really hostile to the female body? There is not the slightest doubt that male hormone is excreted in the urine of normally menstruating and pregnant women, as Womack and Koch (7) demonstrated in 1932. The source of these androgens in the female body is the bisexual gland, the adrenal cortex, though the ovary itself may produce some male hormone-like principles. The androgens found in the female urine are not mere degradation products of estrogens.

Only very small quantities of androgens can be found in the urine during infancy. During the reproductive life of women about 42–58 international units are excreted in the urine daily. Men excrete 63–68 international units, and after the menopause 70 and more international units can be found in the female urine daily. The international unit is equivalent to 0.0001 gram of crystalline androsterone and 1 mg. testosterone propionate is equivalent to 50 international units. The daily excretions of androsterone in the female urine fluctuate; brunettes excrete more than blondes, but all of them, from the cradle to the grave, excrete androgens irrespective of their age, complexion and race.

After all, one cannot say that male hormone is foreign to the female body, but is it not hostile to the female organism if artificially administered?

Male hormone sometimes shows gynaecogenic properties and can be synergistic to the twin hormones, oestradiol and progesterone, the products of the corpus luteum. But in the usually administered doses, as well as in massive doses, it counteracts the twin hormones and shows only antigynaecognic effects.

In the natural state, however, the female and male hormones circulating in the blood exist in a relatively fixed physiological ratio. This ratio is by no means definable. Although we have a method of determining the blood estrogens we have no reliable method for the determination of blood androgens. McCullogh and Osborn and more recently Törnblom have described methods for blood androgen determination. Neither is exact. Törnblom was the first to determine blood androgens in women. The variations in women between 20–29 years seem so great (between 0.4 and 33.8 per 100 cc. of blood) that this method cannot be regarded as a reliable one (82).

But this very ratio of the female and male hormone in the blood and tissues determines the sex characteristics; the texture of the skin, the distribution of hair, the tone of the muscles, the timbre of the voice, the bony structure, the play of the capillaries in the endometrium with the resulting quantity of menstrual flow

and the reaction of breast tissue, and also the female character, psyche and sexual behaviour—in short, the whole make-up of the female body, the eternal feminine.

As long as we do not know and determine this ratio, our therapeutic venture with male hormone remains empirical. From animal experiments no cogent conclusions can be derived, as different species react differently to male hormone.

In the following survey no animal experiments will be quoted, and it should be pardoned if not every one of the authors who have published papers about testosterone during the last ten years is mentioned. Those who stood godfathers to the clinical birth of testosterone in gynaecology are not omitted.

PART 2

Mode of Action

The effect of testosterone propionate on the human endometrium was discovered by the author of this article by chance during the treatment of a patient with chronic mastitis (4). It was, so far as the writer can say, the first systematically examined case, as at that time (April, 1937) no publication concerning the action of testosterone on the human breast or endometrium existed.

The writer quotes here his first clinical investigation from April, 1937 as the first fundamental experience on which all the others were built (4).

Miss B. consulted me because of a lump in the left breast, on March 21, 1937. Her genitals were normal, she had always had normal, regular menstruations, her cycle was 3/28. My diagnosis was chronic mastitis; testosterone propionate treatment was commenced.

Last period	17th March	
180 mg. test. prop.		
Last injection	11th April	41 days.
Missed next period		
Diagnostic curettage	27th April	
		Premenstrual endometrium. Lump in breast regressing.
Next period	4th May	
600 mg. test. prop.		
Last injection	30th May	57 days.
Missed period		
Diagnostic curettage	30th June	
		Atrophic endometrium. Lump disappeared.
Next period	23rd August	
Biopsy	23rd August	
		Normal endometrium in secretory phase.

The patient showed no untoward symptoms during or after the treatment. She continued to have normal menstruations. She married in July, 1939, had her first baby girl (5 lbs.) in March, 1943. She fed the baby for 10 months. I delivered her of her second baby, a boy (nearly 8 lbs.), by means of a Caesarean section in March, 1946. She fed this baby for 5 months. The last examination took place in December, 1947, 10 years after the therapy. The periods remained normal and regular, and no lump has re-appeared in the breast.

From this and later clinical experiments and investigations of Foss (8) it became evident that in normal women:

(1) Testosterone propionate in monthly doses of 100–200 mgs. slowed down the tempo of the normal cyclic development of the endometrium.

(2) Testosterone propionate in monthly doses of 600 mgs. and more arrested the cyclic normal development of the endometrium and rendered it atrophic without exception.

(3) Discontinuation of testosterone propionate administration resulted in normal redevelopment of the endometrium and normal menstrual cycles after a certain time.

There are flowing transitions from the slowing down of the normal endometrial development to the complete inhibition of its growth according to the dosage employed. (The same phenomena in the endometrium are brought about by hypothalamic storms—fear, fright, tension, etc., acting via vegetative nervous pathways directly on the pituitary and the adrenals.)

How can the action of testosterone propionate be explained?

Although the exact mode of action is largely problematical, it could act in any of the following ways:

(a) centrally on the hypothalamic-pituitary release mechanism of the gonadotropes (anti-gonadotropic).

(b) by inhibiting the formation of the follicle or corpus luteum in the ovary (anti-ovarian).

(c) by counteracting the blood and tissue estrogens directly (anti-estrogenic).

(d) by local action on the myo-endometrium (anti-haemorrhagic).

Many authors (1, 4, 6, 8, 9, 11–14) found that gonadotropes in the urine of women who were treated with large or massive doses of testosterone propionate disappear partly or completely from the urine. It is true also at the menopause when as a rule great amounts of gonadotropes are excreted in the urine.

Testosterone therefore acts on the release mechanism in the hypothalamic—anterior pituitary system. Either the production in the anterior lobe of the pituitary may be inhibited or the stored gonadotropic hormone is not released. We do not know the mode of action in the human being. Massive doses of testosterone inhibit also the release of thyrotropic hormone from the anterior pituitary (10), and the release of lactogenic hormone after childbirth (15–17). The male hormone as well as the female hormone may act not only on the different cells in the anterior pituitary. It may act on a higher level, in the hypothalamus, the head ganglion of the vegetative nervous system from which sympathetic and parasympathetic nerve fibres innervate the pituitary gland. The pituitary is under the control of the hypothalamus, the centre for emotional response.

Male hormone in large doses is anti-gonadotropic

Whatever the central mechanism, the effect on the ovary is rapid. The ripening of the follicle in the ovary and the formation of the corpus luteum is slowed down, postponed or completely stopped. Male hormone administration has therefore an indirect inhibiting action on the ovary and slows down or completely inhibits the production of estrogens and progesterone. Greenblatt (18) im-

planted tablets of 400 mgs. of testosterone and for various indications performed a laparotomy a few months after the implantation.   He found fresh corpora lutea. But if greater quantities of male hormone are administered and the laparotomy is performed immediately after the cessation of male hormone therapy no fresh corpus luteum is found.

Testosterone in large doses is anti-ovarian

Does a certain quantity of male hormone neutralize a certain quantity of female hormone, as acid neutralizes alkali in a test tube?

The shrinking non-estrogenic vaginal epithelium of a menopausal woman shows cornification and glycogen deposition in the vaginal cells after treatment with a certain amount of estrogen, as if the menopausal woman had returned to her reproductive span of life.   As soon as a certain amount of testosterone propionate simultaneously is injected, the rejuvenating effect of the estrogen is nullified, and the menopausal vaginal epithelium remains menopausal (19, 20).   25 mg. testosterone neutralizes 0.5 mg. oestradiol (19).   The ratio is 50:1.   This neutralizing ratio is not the same for the endometrium.   Here, according to Ferin (21, 22) 600 mg. testosterone neutralizes 16 mg. stilboestrol.   This ratio is 30:1.   Assuming a monthly production in the normal woman of 15–20 mg. oestradiol— there is a wide range in different individuals—the requisite neutralizing dose of testosterone would be 600 mg.   The ratio would again be about 30:1.   This dose of 600 mg. testosterone which renders a normal endometrium atrophic was previously called by the writer the hormonal atrophying dosage (H.A.D.) for the endometrium, and may be taken as a standard dosage, which must either be decreased or increased according to the desired clinical effect.

The male hormone in large doses is anti-estrogenic

Though moderate doses (150–200 mg.) of testosterone reduce the loss of blood in hypermenorrhoea, they have little effect on the endometrium, which may remain in the same condition as it was before the administration of the male hormone.   If it is estrogenic before the treatment it may remain estrogenic afterwards.   If it is in the secretory phase it may remain so afterwards, but in all these cases the loss of blood during the following period is reduced to a normal one, or in a normal one, to subnormal.

Testosterone has a specific contractile effect on the myometrium (23) in the blood-vessel occlusion.   But, as will be seen in an article to be published by the writer in the near future in the Journal of Obstetrics and Gynaecology of the British Empire, the action is more probably on the endometrial vascular bed itself (81).   If testosterone propionate (125 mg. or more) dissolved in propylene glycol is injected intravenously, the vessels of the endometrium in a majority of cases constrict after a short temporary vasodilatation.

The same phenomenon can be observed more directly in laparotomy, when the uterus is seen to blanch 2 minutes after the injection and to remain blanched for a further 2 or 3 minutes.   It is reasonable, therefore, to assume that more prolonged dosage may produce a similar and more permanent effect.

Testosterone in large doses is therefore anti-haemorrhagic

As we have seen, androgens may have 4 different modes of action. It is not known which of them is the most important or whether one or more actions are synchronized.

Whichever it may be, the question asked in the beginning of this article, whether the male hormone is hostile to the female organism, must be answered in the affirmative without even taking into consideration the unpleasant masculinizing effects androgens can produce in the female body, with which the writer will deal later on.

In spite of this one cannot overlook the fact that androgens act as an antidote if too many estrogenic principles are produced and circulate in the female body, and in logical consequence one should use androgens in real hyperestrogenic conditions. One should not forget also that a surplus of estrogens is hostile to the female body.

As in the vegetative nervous system parasympaticus and sympaticus must be in balance, so in the primitive nervous system—that is the entity of the endocrines—the estrogens and cholinergic-like principles, if the writer may appropriate Dale's expression, must be in balance with androgens, the adrenergic-like principles in the female body.

Estrogens are the steadily, discreetly working principles. They have the upper hand over the androgens under normal conditions. But if they are in excess, they should be counteracted by androgenic principles in order to maintain the endocrine female/male ratio. *For this purpose and for this purpose alone the male hormone should be used in gynaecology.*

With this in mind we have to discuss the clinical application of the male hormone.

PART 3

(a) *Hypermenorrhoea: Menorrhagia, Metrorrhagia*

Numerous authors (4, 8, 11–14, 24–35) have employed male hormone for this condition. Some use small doses of 5–10 mgs. 3 or 4 times during the second half of the cycle for hypermenorrhoea; others begin the therapy in the first half of the cycle. Testosterone therapy should always be started before the follicle ripens or a corpus luteum is formed; the result is more reliable and smaller doses can be used than later when the follicle is already matured.

In cases of menorrhagia and metrorrhagia larger doses of testosterone propionate are necessary. A dosage of 200–300 mgs. monthly in intramuscular injections is advisable, to be commenced just when menstruation is finished, but in cases of severe meno-metrorrhagia up to 400 mgs. can be given. If sublingual tablets are preferred (and this should be the therapy of choice) usually at least 300 mg. up to 500 mgs. can be recommended. Five hundred monthly mgs. of oral testosterone can be administered with impunity in severe cases, especially where there are multiple small fibromyomata. The flooding in these conditions can be well controlled in this way. If one requires a quick result, 4 injections of 25 mgs., each during the first fortnight of the cycle, may be combined with 10

mgs. oral testosterone daily for 20 days.   This sequence should be repeated 2 or 3 times to regulate subsequent menstruations.   In the majority of cases, if there are no submucous fibroids, the patient will benefit for a considerable length of time, and often for years.

One or 2 days after the beginning of androgen therapy there is occasionally some irregular loss of blood due to temporary dilatation of the endometrial vessels, before they constrict.   Recently a method of administering testosterone and progesterone in combination has been recommended (36); testosterone because of its haemostatic properties and progesterone to induce desquamation of a hyperplastic or malfunctioning endometrium.   The bleeding is said to be arrested on the first or second day after treatment has been commenced.   The technique is to give 25 mgs. of testosterone and 10 mgs. of progesterone on 5 consecutive days.

(b) *Fibroids of the Uterus*

Patients with multiple fibroids are frequently relieved by the administration of male hormone.   The menorrhagia and dysmenorrhoea are alleviated and the tumour materially reduced in size, small fibroids apparently disappearing. Amounts of 300–400 mgs. of testosterone monthly, intramuscularly, are necessary.   The results, however, are usually only transitory and this therapy can be recommended only in patients who are poor risks for major surgery.   As preoperative treatment such a procedure is beneficial, especially as these patients regain strength as the blood picture approaches normality.   In premenopausal patients suffering from menorrhagia due to small fibroids it is the therapy of choice, as often they can be tided over until the menopause induces normal shrinkage of the fibroids.   In this way hysterectomy can often be avoided (37, 38, 39).

(c) *Endometriosis*

In endometriosis massive dosage only will help, between 500 and 1000 mgs. monthly being necessary (40, 41).   The disease can be brought to a temporary standstill, but a real cure is unobtainable.   Here also male hormone therapy can be regarded as a predominantly pre-operative and perhaps post-operative measure. However, in cases of widespread endometriosis the patients feel very much relieved, so that testosterone administration is the method of choice in many cases, locally as well as generally.   On the other hand it should not be forgotten that a monthly dose of 400 mgs. or more can bring about masculinizing effects and *one will not find a woman the world over, who would not prefer her disabling floodings, pain, and, if necessary, a mutilating operation to a beard growing on her chin or upper lip and to a low-pitched male voice.*

The administration of male hormone by subcutaneous implantation is of value in this connection.   In 1939 the writer, in the presence of the originator of this method, A. S. Parkes, implanted tablets of testosterone, and was for a long time partial to this method.   Longer experience has, however, shown that oral therapy gives as good though perhaps less rapid results.   Apart from its simplicity

this method has the advantage of easy control, so that symptoms of masculinization can be arrested at their earliest appearance.

(d) *Menopause*

The menopause is not usually accompanied by hyperestrinemia but sometimes large amounts of estrogen are present at this time as a result of the compensatory action of the anterior pituitary and adrenal cortex.   In certain cases androgenic is preferable to estrogenic therapy.   Patients who have or have had cancer for example, particularly breast cancer, should never be given estrogens for their menopausal disturbances; androgens are preferable (42).   The same holds good for patients with a familial cancer history, and for women in whom small doses of stilboestrol provoke bleeding.   In these cases an adequate monthly dose is 100–300 mgs. of testosterone by mouth or 50–100 mgs. by implantation.   All the well known vasomotor symptoms of the menopause subside fairly quickly; hot flushes, attacks of sweating, depression, vertigo and anxiety are relieved.   But these small doses will not control excessive uterine haemorrhages.

In the great majority of cases the estrogens are superior to androgens in the control of menopausal symptoms; the latter should be reserved for those cases where the former are badly tolerated or provoke untoward symptoms (43, 44, 45, 46).

Estrogens and androgens together have been given to menopausal women and the published results (49, 50) are good.   In the writer's experience the optimum combination is a ratio of 10 mgs. methyl testosterone and 1 mg. diethyl stilboestrol, taken every other day.   The male hormone not only prevents a possible estrogenic bleeding but acts as a general stimulant on the general condition, so that the fatigue and many of the nervous symptoms disappear.

The normal female/male hormone ratio is disturbed at the menopause and may more easily be restored with this combined therapy.   But the first essential in treatment is the abolition of distressing symptoms and this is best accomplished by giving as small doses of hormone as possible for the shortest possible time, the treatment being interrupted from time to time, since the final effects of hormone therapy, so far as stimulation of new growths is concerned, are not yet known.

(e) *Premenstrual Tension*

Major premenstrual molimina disappear most abruptly with the onset of menstruation and may be followed by hypermenorrhoea or hypomenorrhoea.   Many of the distressing symptoms are said to be caused by hyperestrinemia, but this is doubtful.   Testosterone has been given on this hypothesis by several authors (32, 33, 47) in a dosage of 10–50 mgs. during the second half of the cycle, and in many cases with considerable relief, but all the symptoms of premenstrual tension, oedema, abdominal distension and emotional stress are adequately relieved by Greenhill's ammonium chloride technique (48)—1 gram 3 times daily 10 days before the onset of the menstrual flow.   There is no justification for the use of

androgens when estrogens, progesterone, ammonium chloride and similar harmless preparations can be used with equal effect.

(f) *Intracyclic Bleeding*

Mid-menstrual bleeding is mostly the result of transitory hyperestrinemia, and calls for treatment only where the bleeding persists more than a few hours or a day.. Oral testosterone in 5 mg. doses given daily throughout the intermenstruum, or 25 mg. hypodermically 4 times in the first half of the cycle, abolished the symptoms without interfering with ovulation (48, 49).

(g) *Dysmenorrhoea*

In dysmenorrhoea, the causes of which are so manifold that they cannot here be enumerated, testosterone therapy seems to have no real place in spite of the good results which have been reported by several authors (51–53) and which the writer has himself seen.   The rationale is based on the suggestion that functional dysmenorrhoea occurs only in the presence of a corpus luteum, and that if this is inhibited the period should be rendered painless.   But the suggested oral dosage of 20 mgs. given daily for 20 days is not large enough to prevent ripening of the follicle and corpus luteum formation.   Whether testosterone in these small doses is able to arrest the peristaltic movements of the uterine and tubal muscles, another cause of functional dysmenorrhoea (54), is more than doubtful.

The difficulty of correct assessment of hormone therapy in these cases is evidenced by the apparently complete and permanent cure in a personal case where normal saline was substituted for the injection of male hormone without the patient's knowledge.   In view of the many and varied factors involved and the success attending safer methods, the routine administration of testosterone to these patients would appear not to be justified.

(h) *Mastopathia, chronic mastitis, fibroadenoma*

The ducts and acini of the breast react to the varying hormonal concentrations during the menstrual cycle.   Both show marked premenstrual hypertrophy with regression of the ductular epithelium and reduction in the acinar size at menstruation, i.e., when the blood estrogen and progesterone content is at its lowest.   If the estrogen blood level is raised, premenstrual mastalgia may result. Hyperestrinemia may bring about chronic mastitis, the breasts presenting nodules or small cysts from the size of a pea to that of a pigeon's egg.

Androgens may be employed to counteract the estrogen surplus in these cases. The effectiveness of androgens may be due to a direct action on the breasts, as local androgen administration in the form of ointments or androgen suspension in alcohol can bring about the desired effects.

It is often striking to observe the promptness with which this therapy will alleviate the symptoms of both true mastopathia and chronic mastitis, the cystic changes of the latter undergoing rapid regression (2, 3, 4, 9, 11, 58).   The dosage recommended is 250 mgs. monthly equally distributed throughout the period and repeated once or twice in subsequent cycles, for otherwise relapse is common.

Dosage supervision is necessary, however, for testosterone in this quantity often interferes with ovulation, and masculinization is an ever present danger in spite of the hyperestrinemia which is the basis of all these cases.

(i) *Sterility*

In some cases of sterility with no organic lesion there is secreted in the mid-menstruum an abundant viscid, glary cervical mucus. This discharge is acid and hostile to spermatozoa, which cannot penetrate it. But it can be considerably diminished if testosterone is given in small daily doses, up to a monthly total of 150 mgs., during the first half of the cycle, and resulting conception is by no means infrequent. Excess cervical mucus, in the absence of cervicitis, is usually the expression of a hyperestrinemia. Testosterone would in these cases be the logical counteracting agent (55) and is worthwhile trying.

(j) *Frigidity*

One cannot discuss within the framework of this article the complex question of absolute and relative frigidity. Estrogens and androgens have been given empirically for its relief (56) and there is no doubt that the latter almost universally produces an aphrodisiac reaction when given in large doses (57) (Last comprehensive review 10th Congress Français du Gynécologie, 1946). It acts locally by stimulating enlargement of the clitoris, an effect which may also be produced by the topical application of testosterone ointment, but it may also increase the sexual drive. This increase in libido is, however, purely temporary and the aphrodisiac effect of male hormone should not be a medical indication for its employment, for the dangers of masculinization more than offset any temporary stimulation. The psychic effect is a real one, and can be a source of considerable embarrassment in elderly women undergoing testosterone therapy for some other condition, e.g. breast carcinoma (27).

(k) *Disturbances of Micturition*

The French authors, Mocquot and Moricard, (1) were the first, as far back as 1936, to use male hormone in functional troubles of micturition in women, especially nocturia, with good results. The genito-urinary system is probably under estrogenic influence. We know this from the disturbances which occur during pregnancy and during the menopause, where probably not an estrogen deficit but an estrogen surplus is the cause. Castration cases and menopausal amenorrhoea sometimes show an increased estrogen level, when anterior pituitary and the adrenal cortex are hypercompensating. The male hormone may increase the maximal intravesical pressure, and may act on the kidney itself or on the water balance and the electrolyte metabolism.

In cases where fibroids are associated with frequency of micturition one should attribute the good results after male hormone therapy not only to the action of testosterone on the urinary system itself, but more to the action on the fibroid. Nocturnal frequency can well be alleviated by testosterone doses up to 400 mgs. without fear of arrhenomimetic phenomena (59). Familial enuresis in children can be arrested (60).

PART 4

Other Clinical Indications

(1) Pelvic Inflammatory Disease.

Male hormone therapy is of value in chronic pelvic inflammation because of its property of suppressing the menstrual flow and so diminishing congestion. This is particularly true when menorrhagia is a prominent symptom. Doses up to 650 mgs. monthly have been given with good effect (61), but virilism may be an unwelcome accompaniment unless closely supervised. This method would appear to be particularly indicated in tuberculous adnexitis, but there is no record so far of its application to this condition.

(2) Hyperemesis gravidarum.

In early pregnancy, by contrast with the later months, women react to moderately small doses of androgens, and good results have been obtained by their administration in cases of hyperemesis (62), particularly when the vomiting is accompanied by a high estrogen blood level.

(3) Suppression of Lactation.

Androgens are capable of suppressing lactation in the same way as estrogens, i.e., by their inhibiting action on the release of the lactogenic hormone from the anterior pituitary (9, 15, 16, 17, 63, 64, 65). Treatment must be commenced immediately after delivery, as established lactation remains unaffected, even by extremely high doses (500 mgs.). Some authors have succeeded in preventing lactation with small monthly doses of 100 mg., others used up to 250 mgs.

The advantage of testosterone over estrogen for this purpose is that the former does not delay either myometrial or endometrial involution (66), while estrogen does. Male hormone delays the regeneration of the surface epithelium in the uterus (67). Testosterone also appears to exert a more rapid and complete effect on the painfully engorged breast. Lastly, its symptom withdrawal curve is much less steep, so that a more prolonged effect is obtained and recrudescence of lactation, which is so commonly seen after stilboestrol suppression, is avoided.

It cannot, of course, be too strongly emphasized that the artificial inhibition of lactation is blatantly unphysiological, and should not be undertaken except for the strongest indications. Apart from the obvious general physical and psychological effects of its interruption, quite apart from the adverse influence on the child, there is definite evidence that the practice is locally cancerogenic, particularly where the suppression is incomplete. It is established that cancer of the breast was extremely common in Chinese women of the Mandarin class during the Ming period, who, abhorring large breasts, avoided lactation and handed over the newborn to their wet-nurses, among whom the incidence of breast cancer was very low. The cause of the malignant change probably lies in the artificially continuous hyperestrinemia, since the women had children in quick succession, but whatever its pathological basis, the risk is a very real one.

If lactation *must* be suppressed, male hormone is preferable to stilboestrol for

the reasons given above, and also for the possible cancerogenic effect of the latter, particularly when there is a familial cancer history. There is little danger of virilism, for puerperal women seem curiously resistant to this complication.

(4) Prematurity.

The full term infant carries out with it a relatively high concentration of sex hormones, which are correspondingly deficient in the premature child. Male hormone given intramuscularly appears to be remedial, stimulating metabolism and causing a rapid gain in weight (68).

PART 5

General Actions of Male Hormone

(1) Effects on the blood calcium.

A single injection of 20 mg. testosterone raises the blood calcium within 2 hours without changing the urinary output of phosphates (69). The reduction in the urinary excretion of inorganic phosphorus, potassium and creatine after testosterone application points to a somatotropic influence of androgens (70). Early epiphyseal closure in young girls who are subjected to androgen treatment could result. Young girls should not be treated with large amounts of androgens.

On the other hand the hormone favours callus formation and calcium deposition after complicated and malunited fractures (71) and has favourable effects in osteoporosis (72). This fact will be discussed later when the gratifying effect of testosterone on the bone metastases of breast cancer is described.

(2) Effects on the haematopoetic system.

Testosterone has a stimulating effect on the bone marrow. The number of erythrocytes and haemoglobin are increased, especially in cases in which normocytic and hypochromic anaemia complicate hypopituitarism (72, 73). The blood creatine is similarly raised and the sedimentation rate accelerated in the majority of cases after the fourth month of pregnancy (75).

(3) Metabolic Effects.

Testosterone induces nitrogen, sodium and water retention and raises the basic metabolic rate. The retained nitrogen is transformed into protein with resultant increase in body weight.

(4) Effects on hypopituitarism.

Testosterone has been used with very good result in the posttraumatic and postpartum haemorrhage syndrome known as Simmonds' disease (74). These cases show loss of sexual function, amenorrhoea, loss of libido, usually sterility, low basal metabolic rate, low excretion levels of follicle-stimulating hormone and extremely low excretion of 17-ketosteroids, apart from the common asthenia. Twenty mg. male hormone given weekly for 20 weeks improves these conditions very much. As mentioned above, the hypochromic anaemia complicating hypo-

gonadism and hypopituitarism is improved and testosterone seems to enable the marrow to utilize haematinic principles and restore the cellularity to normal.

Patients with Cushing's syndrome and Addison's disease react after testosterone in similarly favourable manner.

(5) General stimulative effect.

There is a curious side effect which may be noted in most cases undergoing male hormone therapy, an improvement of the blood picture, an appreciable gain in weight and general increase in visceral muscle tone. With this observation as a basis, the author of this article has made it a practice for the last 2 years to give male hormone intramuscularly as a routine in doses of 10–20 mgs. for 7 to 10 days in postoperative hysterectomy (because of fibroids) and post-delivery cases, particularly when undue haemorrhage has been a complication.

<div align="center">PART 6</div>

Methods and Disadvantages of Testosterone Propionate Administration

Testosterone is the most potent of all the androgens. It is prepared commercially from cholesterol. Esters of testosterone, especially that of propionic acid, surpass free testosterone in activity. The propionate is therefore the form commonly employed. The route of administration is usually by intramuscular injection. It can be given also by inunction ointment or in alcoholic solution, especially when a more local effect is desired (i.e., in mastitis), but in this form its action is very weak. As sublingual tablets (methyl testosterone) it can be given by mouth with very good effect.

Testosterone is rapidly absorbed by the gastrointestinal tract and secreted in the urine and feces. There is usually an increase in the urinary androgens after administration of large doses of testosterone.

Ethynyl testosterone (pregneninolene) is less effective but has no anti-gynecoganic nor arrhenomimetic qualities and does not inhibit the activity of the anterior pituitary lobe. It is relatively easily absorbed through the skin.

Pellet and tablet implantation have been widely employed. The absorption rate depends on the size of the implantation (27, 77), propionate tablets losing 0.85 per cent of their weight daily, pure testosterone 1.18 per cent (78).

Crystalline testosterone can be given by intramuscular injection as an aqueous suspension of 20 mg. to the ccm. It has the advantage of being painless (79). Vaginal and rectal suppositories containing 25 mg. of the hormone can be of value.

In the writer's opinion, the route of choice in the great majority of cases is the oral. Whether we deal with estrogens or androgens, neither of which is indifferent, and sometimes harmful, the method of administration must be easily controllable in order not to transgress the borderline where more damage than benefit results. With oral therapy we can stop at any time, and right on time, as soon as we think we may have transgressed this borderline.

<div align="center">*Drawbacks of Androgen Therapy*</div>

Androgen therapy is a two-edged knife. Many disabling symptoms may be rapidly and often completely relieved, but over-dosage can cause much damage,

reversible damage, it is true, but still very unpleasant. Hypertrichosis, acne, voice changes, enlargement of the clitoris and undesired increase of libido, are fairly easily produced and inevitably provoke secondary psychological symptoms. In the writer's opinion, based on approximately 1500 cases in the literature and also his own cases (80) the maximum permissible monthly dose is 350 mgs. by injection and 600 mgs. by mouth. This should not be transgressed per month, indeed it should be considerably diminished for patients in whom there is already a tendency to hirsutism. The best control over androgen therapy would be the determination of the estrogen-androgen ratio in the blood, but we are still very far from this goal. The determination of urinary estrogens and androgens is unsatisfactory and of little help in the majority of cases. The metabolism of the androgens in the female body is not completely known.

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PART 7

Cancer of the Breast and Androgens

Estrogens are growth hormones and the female breast responds cyclically to their rhythmical release. Mastopathia, chronic mastitis and fibroadenoma are pathological products of an abnormal reaction to this growth hormone. Androgens, although they may contain a growth element themselves, counteract this hyperestrogenic stimulation, as has been described previously. If cancer of the breast is the pathological end-product of an abnormal reaction to hyperestrogenism, and there is a reasonable basis for the hypothesis, there is here a clear indication for androgen therapy.

In 1938 and 1939 the writer published the first articles (1, 2) about androgen therapy in cancer of the breast. Ulrich (3) published one case of breast cancer treated with androgens. While testosterone had no effect on the very advanced primary tumour itself, temporary amelioration of these hopeless cases was undeniable. But further clinical and experimental experience induced the writer to recommend the implantation of large doses of testosterone twice or thrice yearly after total mastectomy as postoperative prophylaxis to prevent recurrences (4, 5). The male hormone therapy must be continued for years, with yearly doses up to 3000 mgs. or more.

This method was checked by Prudente (10) and Adair (14) is going to try the value of this prophylactic method.

Because of the scarcity of testosterone during the war no further cases of breast cancer could be treated here and the writer's series remained small. But in America from 1942–1947 many surgeons took up and developed these ideas. Farrow (7) used testosterone in the treatment of breast cancer and he studied the action on serum calcium and on skeletal metastases from breast cancer. Unfortunately he used only small quantities and had no results. He even saw an unfavourable effect with the doses he administered on skeletal metastases. The small doses of testosterone employed favoured a hypercalcaemia. Fels (8) reported temporary but striking improvements after massive doses, subsidence of pain, disappearance of vomiting and palpable nodules, and for the first time improvement of the radiological picture of the skeletal metastases, a fact which was confirmed by Adair in 1947 (14).

Abel (9) tried the same therapy in malignant disease of uterine carcinoma with striking temporary improvement. The writer saw temporary improvement in inoperable carcinoma of the ovary in 2 cases (42 and 43 years of age), but no improvement in a patient of 65 years.

Prudente (10) reported on 127 patients with operable tumours localized in the breast with or without axillary metastases. Sixty-four were treated with radical mastectomy alone and 63 underwent mastectomy with testosterone propionate treatment postoperatively. The weekly dosage varied from 25–175 mgs. and was continued over years irrespective of whether virilism resulted. The results

in the patients who had received male hormone were definitely better than in those of the other group. Of the former 90.4 per cent survived without recurrence for 3 years or longer as compared with only 46 per cent of the untreated patients. Prudente had the impression in his large series (which the writer gained in his small series years ago) that postoperative testosterone treatment gives very good results.

Herrmann and Adair (12, 13) reported on patients with soft tissue metastases treated with testosterone propionate doses up to 7000 mgs. for 6 or 7 weeks. One of 3 patients showed an appreciable regression of the metastatic soft part tissue, the other 2 did not react. In 3 other patients who received 3000–4000 mgs. the treatment was not effective. The androgen therapy did not influence the radiosensitivity of the carcinoma, but in most instances an increase of weight in the patients was very marked.

Adair (14) treated patients with bone metastases reserving a total of 2400–3000 mgs. testosterone for 8 to 10 weeks. The blood calcium in cases of advanced bone metastases and bone destruction is 10 to 12 and even 17 mgs. per 100 cc. and comes slowly back to normal after calcium is redeposited in the destroyed area. Alkaline phosphate is necessary for bone repair. The normal limit is 3–5 milligrams. During bone repair under testosterone it goes up at times to 15 milligrams. The areas of bone destruction are filled in with dense callus similar to that seen following X-ray therapy. It is according to Adair more efficacious and longer lasting and more practical than X-ray therapy. If testosterone, according to Adair, has a place in the treatment of recurrences after radical mastectomy it is in young women with grade 2 or 3 growth. Testosterone "is not a cure for breast cancer; its effects are very profound and gratifying." Chase (15) also warmly recommends the use of testosterone for breast cancer in certain conditions. McClure and McGraw (16) have treated 15 patients suffering from breast cancer with male hormone. All but 2 patients showed some symptomatic improvement and were temporarily markedly improved. In 2 there was improvement of cutaneous and subcutaneous nodules. The experience of these authors parallels that of Adair. There was very slight improvement of bone metastases in 4 or 5 patients. The doses used were 100 mgs. 3 times a week for 10 weeks.

Explaining the action of male hormone on breast cancer, the starting point could be the hypothesis that the physiological fixed female/male ratio in the blood and tissues is disturbed either in favour of the female or in favour of the male hormone. A surplus of one of these hormones may be the *causa movens* or *causa remota* of cancer development.

The greatest number of women developing breast cancer is found in the 45 year age group at the average time of the onset of the menopause, when the female/male ratio begins to be disturbed. The ovary fails to respond to the stimulation of the gonadotropic hormones, and the hypercompensating mechanism in the anterior pituitary replaces the falling amounts of ovarian estrogens by hyperproduction of new estrogenic principles in the adrenal cortex, so that the estrogen blood level is not necessarily lowered. It may even be raised.

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Cancer of the Breast and Androgens

Estrogens are growth hormones and the female breast responds cyclically to their rhythmical release. Mastopathia, chronic mastitis and fibroadenoma are pathological products of an abnormal reaction to this growth hormone. Androgens, although they may contain a growth element themselves, counteract this hyperestrogenic stimulation, as has been described previously. If cancer of the breast is the pathological end-product of an abnormal reaction to hyperestrogenism, and there is a reasonable basis for the hypothesis, there is here a clear indication for androgen therapy.

In 1938 and 1939 the writer published the first articles (1, 2) about androgen therapy in cancer of the breast. Ulrich (3) published one case of breast cancer treated with androgens. While testosterone had no effect on the very advanced primary tumour itself, temporary amelioration of these hopeless cases was undeniable. But further clinical and experimental experience induced the writer to recommend the implantation of large doses of testosterone twice or thrice yearly after total mastectomy as postoperative prophylaxis to prevent recurrences (4, 5). The male hormone therapy must be continued for years, with yearly doses up to 3000 mgs. or more.

This method was checked by Prudente (10) and Adair (14) is going to try the value of this prophylactic method.

Because of the scarcity of testosterone during the war no further cases of breast cancer could be treated here and the writer's series remained small. But in America from 1942–1947 many surgeons took up and developed these ideas. Farrow (7) used testosterone in the treatment of breast cancer and he studied the action on serum calcium and on skeletal metastases from breast cancer. Unfortunately he used only small quantities and had no results. He even saw an unfavourable effect with the doses he administered on skeletal metastases. The small doses of testosterone employed favoured a hypercalcaemia. Fels (8) reported temporary but striking improvements after massive doses, subsidence of pain, disappearance of vomiting and palpable nodules, and for the first time improvement of the radiological picture of the skeletal metastases, a fact which was confirmed by Adair in 1947 (14).

Abel (9) tried the same therapy in malignant disease of uterine carcinoma with striking temporary improvement. The writer saw temporary improvement in inoperable carcinoma of the ovary in 2 cases (42 and 43 years of age), but no improvement in a patient of 65 years.

Prudente (10) reported on 127 patients with operable tumours localized in the breast with or without axillary metastases. Sixty-four were treated with radical mastectomy alone and 63 underwent mastectomy with testosterone propionate treatment postoperatively. The weekly dosage varied from 25–175 mgs. and was continued over years irrespective of whether virilism resulted. The results

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The second highest peak in the development of breast cancer is in the 60 year age group.   Is there a new and corresponding disturbance in the female/male hormone ratio at the close of the menopause as there was at its onset and does this change tend to male hormone preponderance?   One thing is certain, that the menopausal urine contains a higher quantity of androgens than before. In women over 60 years also, suffering from breast cancer, female hormone rather than male hormone influences the growth, the latter having no effect or sometimes even stimulating effect in this age group.

It is reasonable to suggest therefore, that the preponderant hormone may be an agent, *causa movens* or *causa remota*, favouring the particular malignant change in the appropriate organ.   To the author's knowledge the blood estrogen content has not been determined in cases of breast carcinoma and the determination of the blood androgens is a relatively new and uncertain procedure.   But one clinical fact is relevant in this connection and that is, that to secure any appreciable effect on breast cancer or its metastases massive doses of male hormone must be administered.   The size of this dose may be gauged from the fact that a preponderance of at least 50:1 must be secured for testosterone propionate to counteract the female hormone in conditions where the estrogen level is normal.   In hyperestrogenic conditions the ratio difference must be comparatively enormous, an assumption verified by the practical findings described above.

PART 8

Conclusions

Within a decade the application of male hormone therapy to gynaecology and other special branches of medicine has assumed a position of paramount importance.   New forms of treatment come and go with bewildering rapidity, but the permanence of the particular one under review remains without question.   Its benefits, however, are by no means unalloyed, and it is sometimes difficult to steer between the Scylla of relieving distressing hyperestrogenic conditions, and the Charybdis of masculinization resulting from treatment.   But a *via media* can be found.   Male hormone therapy can be advised in all forms of hyperestrinemia in adult life.   When used in younger women it should be only a very temporary form of therapy and the dosage must be moderate.   *Minute doses of male hormone stimulate femininity, moderate doses depress, and massive doses completely antagonize it.*

Androgen therapy in breast cancer cannot up to now be regarded as a cure, but it is certainly helpful for the bone metastases and pain.   It remains to be seen whether or not it will have any value as a postoperative prophylactic.

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extravasation and desquamation. Such a corpus luteum as this is not normally found in this state of the cycle.

Specimen No. 332, obtained on day 14 of bleeding, showed in some regions granulosa lutein cells which evidenced few regressive changes. These cells appeared histologically similar to functioning cells. Other cells showed more regression, but none evidenced more degeneration than was frequently observed on day 1 to 5 of normal menstruation. This "irregular" regression of the corpus luteum was an exaggeration of the normal. That the corpus luteum had continued its function was shown by the presence of some secretory glands in the endometrium. Other glands in this still bleeding endometrium had regressed or desquamated and were of postmenopausal type. This specimen indicates without doubt that prolonged life and function of the corpus luteum does occur; that when it regresses it does so slowly and irregularly; and that it is a basic and fundamental part of so-called "irregular regression" of the endometrium and functional bleeding from a progestational endometrium.

Specimen No. 334, obtained on day 8 of bleeding, had a corpus luteum which had persisted without much evidence of degeneration. It was large, still vascularized, the granulosa lutein cells were intact, and connective tissue was scant. The endometrium in most regions contained glands of secretory type. Those portions of the glands that had not been desquamated were regressing. In other regions the endometrium was of postmenstrual type, and was covered with surface epithelium. Prolonged life and function of the corpus luteum was apparent. Irregular and prolonged regression of the endometrium was a direct response to irregular and prolonged corpus luteum degeneration.

Specimen No. 293, obtained on day 45 of bleeding, confirms McKelvey's observation that the longer the duration of bleeding the greater the variation in the endometrial pattern. The endometrium in one portion was covered with intact surface epithelium and contained glands evidencing active secretory function. There was a great amount of intercellular fluid. Other portions of the endometrium were desquamated and bleeding. Still other portions were covered with newly regenerated epithelium and had nonsecretory postmenstrual type of glands. The associated corpus luteum was small, but was typical of a postvascular stage from a histologic standpoint.

Near the termination of a bleeding phase in this type of functional uterine bleeding there are certain typical findings. Specimen No. 265, obtained on day 11 of bleeding, consisted of a small corpus luteum in which many granulosa lutein cells were degenerated, but a few retained their large size, even staining cytoplasm, intact membranes and round or oval nuclei. However, these cells represented a small portion of the granulosa lutein layer. The general picture was one of degeneration. The functional capacity of such a corpus luteum is nil, but its life cycle has obviously been prolonged. The endometrium had been repaired in all but a few small regions, and was typical of a proliferative phase.

These specimens would indicate that functional uterine bleeding does occur from an endometrium evidencing progestational characteristics. The corpus luteum life cycle is altered from normal in that life and function are prolonged.

ENDOCRINOLOGY

STUDIES OF THE HUMAN CORPUS LUTEUM; CORPUS LUTEUM-ENDOMETRIAL RELATIONSHIPS IN FUNCTIONAL UTERINE BLEEDING

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The writers present a histologic study of corpora lutea and endometriums in two instances of functional uterine bleeding, and discuss the relationships of these two tissues. It is their belief that "functional uterine bleeding" can occur and that the ovarian and endometrial tissue changes are identical, irrespective of the presence or absence of gross pelvic pathology, and that it is not logical to exclude cases of such bleeding from the classification of "functional" merely because of the presence of pathology.

The specimens studied were obtained by hysterectomy and oöphorectomy or by resection of the corpus luteum. The operations were performed during the bleeding phase.

In all of the specimens the bleeding was from an endometrium of progestational type. A corpus luteum was present in the ovary in each case. The relationships of the corpus luteum and endometrium were not the same in all specimens. There were 2 distinct types. In one group the corpus luteum appeared to vary from normal, the abnormality consisting of a prolongation of life and function of the corpus luteum. In response to the abnormal corpus luteum stimulation, the endometrium evidenced characteristic changes that have been described previously as "irregular shedding," "irregular regression," and "mixed type."

In the second group the corpus luteum and its functional activity appeared normal. The endometrium evidenced normal responses to the corpus luteum stimulation except in small localized areas. It was from these localized regions that failed to respond that the bleeding occurred.

The writers discuss the specimens in the sequence described above. There is quite conclusive indirect evidence that the life and function of the corpus luteum may be prolonged without alteration of gross characteristics from normal and without cyst formation. In the present study microscopic characteristics of the corpus luteum during various stages of its prolonged life are described. The earliest phase in the cycle in which undoubted prolongation of life of the corpus luteum was observed was in a specimen (No. 335) obtained near the onset of bleeding. The corpus luteum was maintained in the vascular stage with little evidence of degeneration on day 27. That bleeding was about to begin was evidenced by involution of the endometrium and small local superficial regions of

certainly not functional. In some cases, again, both anatomic and physiologic factors may be concerned.

The entity spoken of as "irregular shedding" of the endometrium constitutes one type, but not the only one, of so-called "mixed endometrium." Its occurrence has been well established by a good many investigators, and the generally accepted explanation is that it is due to abnormally prolonged progesterone effect. While this view has been deduced from study of the endometrium, the present authors confirm it by study of the corpora lutea.

That functional bleeding may occur from a progestational type of endometrium has long been known, and little is known as to the mechanism in this ovulatory form of bleeding, in contrast with the anovulatory type, often spoken of as metropathia hemorrhagica. Concerning the latter, we do know something, though perhaps not a great deal has been added since the publication of Schroeder in 1915, at least as regards histological correlations.

All sorts of theories have been suggested to explain the ovulatory forms of bleeding, and it seems probable that the cause is not always the same, and that any one of the links in the ovulatory menstrual mechanism may be involved. The studies of Brewer and Jones suggest that abnormalities of corpus luteum function probably explain at least some cases.

There is still much to learn about the endocrinology and even the cyclical histology of the endometrium and ovaries. It is not always easy or safe to use histology as a criterion of function. There is already an abundance of evidence to indicate that the bleeding cycle in the endometrium does not necessarily parallel the histological cycle, and the work of the authors adds further support to this view.

Finally, as I have repeatedly urged in these pages as well as in other publications, one can not assume any given endocrine effect simply from knowing the endocrine dosage involved, or the histological status of the gland producing the hormone. There is always another and much more intangible factor to be reckoned with, and that is the degree of sensitivity or refractoriness of the recipient tissue. This point likewise is emphasized by some of the observations made by Brewer and Jones.—Ed.)

THRESHOLD BLEEDING AND THE SEX SKIN IN THE CASTRATE FEMALE CHIMPANZEE

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The similarity in chemical structure of adrenal and sex hormones and the presence of sex hormones in the urine of castrates have intrigued many with the possibility of participation by the adrenal glands in the control of cyclical genital activity.

The report of Clark and Birch (1946) that variations occurred in the size of the sex skin swelling of the hysterectomized and oophorectomized chimpanzee under constant dosage with follicular and luteal hormones afforded a possible method for further study of threshold cycles.

One chimpanzee, who had been castrated several years previously, was studied. The size of the sex skin swelling waxed and waned despite constant therapy with

As a result the endometrium is shed in an irregular way. The direct cause of alteration of the corpus luteum life cycle is undoubtedly the pituitary.

The second group is composed of those specimens in which the corpus luteum cycle is normal, the endometrium responds normally, and the bleeding phenomena seem to be independent of the corpus luteum or type of endometrium. Specimen No. 257, obtained on day 1 of bleeding, showed a corpus luteum of the postvascular early regression type. The endometrium, except in small regions, was consistent with this stage of life of the corpus luteum. Since a bleeding period had just terminated 7 days before the present period, and since the corpus luteum was older than 7 days, normal ovulation must have occurred during this previous bleeding period. The relationship of corpus luteum and endometrium in regard to secretory development and activity appeared normal. However, portions of the endometrium were bleeding. The bleeding was from large sinuses just beneath the surface. Normal desquamation was lacking. The independence of this bleeding from the corpus luteum was apparent.

Specimen No. 266, obtained on day 16 of bleeding, showed a young corpus luteum whose appearance suggested ovulation had occurred during the 16-day bleeding period. The major portion of the endometrium had responded to corpus luteum stimulation normally and in accord with the histologic development of the corpus luteum. One superficial region of endometrium varied from the overall picture; the surface epithelium was lost, there was scant superficial desquamation of underlying stromal tissues, and blood and intercellular fluid projected into the uterine cavity. The independence of this bleeding from the normal response of the rest of the endometrium was apparent.

Specimen No. 273 was obtained on the sixtieth day of continuous bleeding. The corpus luteum was in the immediate postvascular stage. The endometrium showed progesterone stimulation. One region was denuded of surface epithelium, and slight bleeding was occurring. There was scant desquamation. This region appeared completely independent of corpus luteum function.

The bleeding in this second group of specimens is not typical of normal menstrual slough and bleeding, but rather seems to be from vascular sinuses without much tissue loss or local tissue reaction. The writers state that in this particular type of functional uterine bleeding the factors responsible are not dependent upon either the histologic type of the endometrium or the corpus luteum. From the present study, it is apparent that ovulation may occur during a period of abnormal bleeding, that corpus luteum development may progress normally, and that the endometrium may respond normally and continue to develop normally. The phenomena that occur to produce the abnormal bleeding in such instances are not known. The explanation may reside in a local bleeding factor in the endometrium or in the local abnormality of response of the endometrium. 21 figures.

(No one will dispute the authors' statement that the presence of pelvic pathology in a case of bleeding does not necessarily exclude the case from the category of functional bleeding. As only one example, the bleeding in a patient who has a myomatous uterus may be purely functional, the tumors being merely coincidental. In other myomatous cases, especially those of submucous variety, the bleeding is usually the direct result of the tumors, and

Injection of an excess of lactogenic hormone at the same time that LH was introduced prevented cholesterinization of the corpora lutea. Thus, it appears that whether or not cholesterol storage occurs depends upon the ratio of LH/luteotrophin. LH appears to have a specific action in increasing the cholesterol store in luteal tissue, whereas the degree of luteotrophic stimulation determines the rate at which the cholesterol is utilized in the secretory process. The observations add to the body of evidence which indicates that cholesterol is a precursor of progesterone. 3 figures.

THE FORMATION MECHANISM OF OESTROGENIC HORMONES; THE PRESENCE OF AN OESTROGEN-PRECURSOR IN THE RABBIT OVARY

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The writers have demonstrated the presence of a cholesterol type—probably identical with cholesterol—in the interstitial gland and in theca interna of the rabbit ovary. During estrus, pregnancy and pseudo-pregnancy, it is stored in the cells in large amounts, while the immature or anestrus ovaries show either none or only very small amounts. The majority of the sterol is present in the form of ester. It is biologically inactive.

In case of coitus or injection of gonadotrophic hormone, the sterol is mobilized from the ovaries. If an intense gonadotrophic stimulation is applied, this mobilization may be completed within some few hours, and the amount of sterol falls from high to very low values. This indicates that the sterol is intimately connected with the formation of estrogenic hormones.

These results suggest that the demonstrated sterol is the precursor of estrogenic substances formed in the rabbit ovary. 4 figures.

(Estradiol is the form in which the estrogenic hormone is thought to be given off by the ovary. The present study, however, deals with the antecedents of this estrogen, and suggests that cholesterol, often spoken of as the mother steroid substance of the body, may possibly be converted into estrogen in the ovary itself, an interesting observation if it can be confirmed.—Ed.)

estrogen and progestin and similarly periodic menstruation occurred. The time relations of these cyclical changes appeared totally unrelated. This asynchrony in the 2 end organs is difficult to reconcile with the theory that such periodic changes are due to fluctuations in the output of sex hormones of adrenal origin. It seems reasonable to conclude that the threshold cycles in the chimpanzee are due to periodic alterations in threshold of the responding organs. It is probable that this same explanation can be applied to threshold cycles in other species as well. 1 figure.

(The observation reported in this paper is a most interesting one, with possible applicability to other human endocrine phenomena as well. The sex skin swelling has been in the past looked upon as a part of the normal reproductive cycle, and has been thought, I believe, to be a purely hormonal one. And yet, in this "oöphorectomized chimpanzee," the sex skin cycle apparently proceeded quite independently of the uterine histological and bleeding cycles induced by estrogen and progesterone. As the author states, the only rational explanation would seem to be that the two end organs have different thresholds of responsiveness to the hormones. In the study of endocrine responses, one is apt to think only of the dosages of hormones, and to forget that the recipient tissues have widely differing degrees of receptivity or refractoriness to the endocrines employed. Among many other examples which might be offered, a normal amount of circulating estrogen can at puberty produce in one girl a normal degree of breast development, in another an enormously exaggerated growth response (abnormal puberal breast hypertrophy), and in still another almost no development, the breasts remaining almost flat.—Ed.)

HORMONAL FACTORS RESPONSIBLE FOR DEPOSITION OF CHOLESTEROL IN THE CORPUS LUTEUM OF THE RAT

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As a result of this study, the writer found that rich deposition of cholesterol occurred in the corpora lutea of the pregnant rat 48 hours after injection of estradiol benzoate or after implantation of small estradiol crystals. Slight accumulation was in progress 24 hours after estrogen administration, but the major change coincided approximately with induced ovulation (ca. 36 hours). The presence of the hypophysis was essential.

Sheep LH injected on the fifth day of pregnancy regularly caused both ovulation and cholesterol storage in corpora lutea within 18 hours, even when the hypophysis was removed at the time of injection. However, if the gland had been excised 24 hours or more earlier, neither event took place. In hypophysectomized rats in which corpora lutea were maintained by LH-free lactogen, injection of LH caused cholesterol accumulation, while administration of estradiol benzoate failed.

hernial sac. The larger portion of the gonad was well differentiated ovarian stroma, with several corpora albicantia. No growing follicles or ova were seen, but there was a Walthard cell rest in one section. The testicular portion of the gonad contained definite testicular tubules in varying degrees of degeneration. Hyalinization and fibrosis were rather marked. No evidence of spermatogenesis was seen. Between the tubules there were masses of interstitial cells of Leydig. A well formed rete testis was present.

A thickening of the hernial sac which resembled histologically the spermatic cord or epididymis extended from one pole of the ovotestis.

Biopsies of the left ovary consisted of a portion of normal ovarian stroma, also with corpora albicantia, but no growing follicles or ova. The nodular portion contained a small Brenner tumor.

The rectal polyp contained only rectal glands surmounted by stratified squamous epithelium.

Inguinal hernia was present in 14 of the 40 reported cases of true hermaphroditism. When associated with any sexual abnormality, inguinal hernia should suggest the possibility of some degree of intersexuality.

The fact that the 17-ketosteroid excretion was reduced postoperatively suggested bio-activity in the testicular tissue. The relatively high urinary gonadotrophic hormone values suggested that gonadal failure existed. The inactivity of the ovarian sections was confirmatory. 7 figures.

(The photomicrographs accompanying this paper seem to leave no doubt as to the existence of both ovarian and testicular tissue in this patient, and therefore its addition to the small group of reported cases of true hermaphroditism. In this patient, as in others of the type, the mingling of sex characters, especially those involving the inner genitalia, was not any more marked, and it is often much less marked than is seen in many cases of the much more frequent pseudohermaphroditism. Hormone studies in these intersexual cases have not proved to be of any particular value in their classification. The fact that in this case the 17-ketosteroid excretion showed a definite drop postoperatively seems to justify the suggestion of the authors that the testicular portion of the ovotestis possessed some degree of bioactivity.—Ed.)

CANCER OF THE BREAST AND ANDROGENS

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After a general discussion of the subject and a report of 3 cases of cancer of the breast with bone metastases, the authors draw the following conclusions:

The hormones cannot be considered carcinogenic, since the experimental work carried on in animals cannot be applied to the human being. In spite of the disagreement that still prevails among authorities on the subject, it seems

TRUE HERMAPHRODITISM; ENDOCRINE STUDIES IN
A CASE OF OVOTESTIS

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Although pseudohermaphroditism is not uncommon, the occurrence in one person of one ovary and testis, or an ovotestis, proved histologically, has been reported only 40 times in the literature. The writers present in this paper a case of true hermaphroditism with an ovotestis on the right and an ovary on the left.

The patient was a 36-year-old negro "female" whose chief complaint was a mass between the legs which had increased in size so much as to cause local discomfort. The patient was a twin and was considered a female at birth. Puberty began at 10 to 12 years; mammary development continued until the age of 20, when slow regression began. The patient had scanty "menstruation", lasting 1½ days, with regular cycles. Axillary and pubic hair developed in feminine fashion; from the twentieth year, facial hair began to appear.

Examination revealed a well nourished "woman" with sparse but conspicuous facial hair with masculine distribution. The breasts were well developed but atrophic changes were evident. A large inguinal hernia protruded on the right side. A large phallus (about 3 cm. in length) was present. No labia could be identified and there was no scrotal swelling. The urethral orifice was located about 1 cm. dorsal to the base of the phallus. Rectal examination revealed a granular tag. Cystoscopic examination revealed a normal female urethra without a vaginal orifice or a verumontanum. Kidneys, ureters and bladder were essentially normal on a plain roentgenogram.

Preoperatively, urinary gonad-stimulating hormone assay showed >96 <192 M.U./24 hrs., and >52.8 <100 M.U./24 hrs.; 17-ketosteroid determinations were 7.6 and 7.5 mg./24 hrs.

At operation, the hernial sac contained omentum with a sliding hernia of the pelvic organs. There was a rudimentary uterus with a left fallopian tube and a left gonad appearing to be a small ovary. A node on the ovary was removed and a slice of ovarian tissue taken for study. The right tube extended into the hernia and disappeared in the sac wall. A short distance from its point of disappearance was a nodule which did not grossly simulate the right gonad. The hernia was repaired and the granular anal tag was removed. A later plastic operation to form a vagina failed.

Five weeks postoperatively, 17-ketosteroid determinations were 5, 4.9 and 5.6 mg./24 hrs. Urinary gonad-stimulating hormone assays contained >96 <192 M.U./24 hrs. After 9 months the patient is in good health and further "menstruation" has not occurred.

Histologic examination revealed an ovotestis protruding from the lining of the

THE MENSTRUAL CYCLE LENGTH AND VARIABILITY OF YOUNG ADULT WOMEN

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The writer presents the results of an investigation of 3 groups of student women who kept menstrual calendar records during one academic year. The subjects of the study were 17 healthy freshman women averaging 17.47 years of age, and 2 groups of 26 and 22 healthy junior women averaging 19.69 and 20.18 years of age.

The results of the freshman records yielded 130 cycles ranging in length from 6 to 61 days, with a mean of 28.88 days, and a standard deviation of 7.11 days. The results of 26 junior records yielded 189 cycles ranging from 21 to 45 days in length, with a mean of 30.05 days, and a standard deviation of 4.51 days. The results of the group of 22 juniors yielded 147 cycles ranging from 21 to 47 days, with a mean of 29.86 days, and a standard deviation of 4.19 days. The junior data were taken during 2 different years.

From these results the author draws the following conclusions. The mean cycle length in young adult women is longer than 28 days. There is no significant difference between the mean cycle length of late adolescent and early adult women students. However, there is an appreciable decrease in the variability of cycle length between late adolescent and early adult women students. Increased maturity apparently exerts a stabilizing effect upon cycle length and variability in young adults. There may be occasional large deviations from individual norms, and arrhythmia of the menstrual cycle of healthy young women students appears to be a normal phenomenon.

(The series of cases studied is too small to be of great statistical value, although the results are probably pretty much what one would find in a larger number of patients of this particular age group. Even marked irregularity is so common in patients averaging 17½ years that it is accepted as of no important significance in itself. The majority of such patients are likely later on to fall into a reasonably normal menstrual tempo, and this is indicated by the lessened variability of the menstrual interval in the author's older group. The practical lesson to be drawn from this fact is that such menstrual irregularities in patients otherwise in good health, and with no evident endocrinopathy such as hypothyroidism, need no treatment except reassurance, and in some cases, simple constitutional measures. Under such conditions even complete amenorrhea rarely calls for any direct treatment before the age of 17 at least. And yet thousands of girls each year are subjected to estrogen therapy, oral or even hypodermic, just because they have not yet menstruated at the age of 15 or 16, or just because they menstruate very irregularly at 16, 17 or 18. This, as a matter of fact, is one of the more glaring of the many prevalent abuses of organotherapy.—Ed.)

evident that castration does exert a beneficial though transitory effect on cancer of the breast. No woman who has already been submitted to treatment for the latter disease, should ever be allowed to become pregnant. Androgens undoubtedly have some effect on the breast, since they do yield good results in cases of functional mastopathias as well as in other benign types of tumor. Androgen therapy employed weekly in the form of testosterone, in doses above 50 mg., seems to reduce and even induce regression of metastases for a more or less prolonged length of time, besides acting on the primary lesion as well. It possesses a definite analgesic effect, but does not cure. At the present time, combination of both castration and androgentherapy ought to be considered the best form of treatment for such patients.

(The conclusions reached by the authors are in conformity with the views of probably the majority of surgeons, although there are some who are not convinced of the value or wisdom of castration and do not practice it in their clinics. Nevertheless, it does appear to be a rational addition to the treatment of such patients during the childbearing period. Just why so many surgeons believe that castration is much better than radiotherapeutic abolition of ovarian function, a far simpler method, I do not know, even conceding that the function of certain ovaries is rather hard to kill, so that the therapy may have to be repeated. This disadvantage would not seem sufficiently great to justify the prevalent preference for the surgical plan. There is no question as to the undesirability of subsequent pregnancies, associated as these are with enormous estrogen production, in women who have had breast cancer.

The as yet small number of worthwhile studies on the palliative employment of testosterone in advanced mammary cancer with bone metastases, especially that of Adair at the Memorial Hospital in New York, point to its efficacy. The theory of the method as well as its results appear to be analogous to and comparable with those of stilbestrol in cases of prostatic carcinoma with bone metastases. There is great relief from pain and apparent retardation of the disease, but not of course cure. When testosterone is used, the dosage should be large and prolonged, so that hirsutism, voice changes and other masculinization manifestations are always to be expected, though these may be considered a small price for the patient to pay for the relief of her pain and the possible prolongation of her life.—Ed.)

4 years, 3 years 7 months, 9 years 7 months, 11 years and $6\frac{1}{2}$ years, respectively. The boys' ages were 5 years and $6\frac{1}{2}$ years, respectively. All of these patients had an excretion of gonadotrophin such as is found only after puberty; the values recovered were 16, 25, 12, 8, 22, 7, 13, 17 and 18 M.U./24 hours. Also, the excretion of 17-ketosteroids was above average for the age of the patient, but well below values associated with hyperplasia or hyperfunction of the adrenal cortex. The author states that it is likely that, in such patients, pituitary function as a whole is increased so that not only is gonadotrophin secretion in excess of normal but also the secretion of corticotrophic hormone. In the 2 boys, a little of the androgen may have come from testicular function.

It is highly improbable that there was any pituitary overactivity due to chronic increased intracranial pressure in these cases; first because of the absence of any history of illness which would be likely to affect the pituitary, and also because of the only slightly raised excretion of gonadotrophin.

The writer considers the question of why an otherwise normal mechanism should be awakened at an abnormally early age. On this point no satisfactory explanation seems forthcoming. Novak assumes a chromosomal or genic basis as the most plausible. In one of the author's cases a history of fibroids suggested the possibility of intrauterine action of estrogen upon the fetus.

In 2 cases a "pregnane derivative" was recovered. It seems likely that this derivative is the result of abnormal function of the adrenal cortex. However, it would be fallacious to argue that sexual precocity of the type under consideration is due to abnormal adrenal function, as it is quite possible that the latter is the result of the former.

To describe cases of "constitutional" precocity as being due to "hyperpituitarism" is misleading. The cases described in this report are examples in which a normal mechanism has been set in motion, but prematurely. 2 figures.

This is an excellent review of an interesting syndrome which obtrudes itself into gynecological practice from time to time. The cases of precocious puberty which are directly due to the presence of granulosa cell ovarian tumor are the ones which the average gynecologist has heard and read about more than any other group. When he encounters a case of precocious puberty, therefore, it is only natural that he should at once suspect the possibility of such an ovarian neoplasm, and there can be no criticism of such suspicions, for they are sometimes proved to be correct. If, for example, thorough pelvic examination, under anesthesia if necessary, reveals a very definite enlargement of one ovary, there is good ground for the suspicion of tumor, and a laparotomy would be fully justified. Estrogen determinations are of no decisive value, for considerable amounts of estrogen would be found in either the granulosa cell cases or in the much more frequent constitutional variety. But when laparotomy is done in cases of unilateral ovarian enlargement, a granulosa cell tumor is not always found. In some of my own cases, for example, a follicle cyst or a general cystic enlargement was revealed, with no evidence of neoplasm. I have in quite a number of cases received for diagnosis slides from cases of this sort, revealing no tumor whatever, so that the experience cannot be exceedingly rare. And yet under such conditions as I have mentioned, I believe that exploratory operation is fully justified, assuming of course that adequate preliminary study has been made.

On the other hand, if satisfactory pelvic examination has revealed not the slightest suggestion of ovarian enlargement, it is safe to assume that the precocious sex changes are of constitutional rather than neoplastic ovarian origin. While it may be objected that a tiny,

THE CONSTITUTIONAL TYPE OF PRECOCIOUS PUBERTY

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J. Clin. Endocrinol., **7**: 171–185, 1947

Novak has used the term "constitutional" to describe a type of precocious puberty for which no adequate cause has been found. This means that all the known conditions associated with sexual precocity have been excluded in the cases in question. The author enumerates the 5 generally accepted causes of sexual precocity, other than that of the "constitutional" type, as follows:

(a) Granulosa-cell tumor; 16 cases have been recorded in association with precocious puberty. Menstruation in these patients is estrogen-induced and anovulatory.

(b) Sexual precocity of the cerebral type; 17 cases have been recorded, in all of which lesions of the hypothalamus and third ventricle were present.

(c) The possibility of adrenal cortical involvement must be considered. In girls, hyperfunction of the adrenal cortex is almost always accompanied by virilism, but 17 cases are on record in which menstruation either preceded or occurred simultaneously with sexual precocity symptoms. These cases are tabulated. In 3 cases menstruation and breast enlargement *preceded* development of any signs of virilism.

(d) The gonadal group; in 21 of 25 cases of precocious menstruation reviewed by Elterich, he found tumors or cysts of the ovaries. Fischer reported an additional case.

(e) McCune describes a group of cases in which sexual precocity was associated with bone cysts and pigmented nevi (xanthomatosis?). McCune described one case and Albright added 5 similar cases. The author suggests that these bone cysts might have been associated with a Hand-Schüller syndrome, and that pressure on the hypothalamus gave rise to sexual precocity.

Elterich encountered one instance of "constitutional" precocity; Novak reported 9 cases of his own, Werner 2 and Craven one. With the possible exception of one case described by Young, the author knows of no instance of this type of precocity in boys; 2 are described in the present report.

Reference is made to the fact that girls with the "constitutional" type of sexual precocity ovulate, while those with granulosa-cell tumor do not. Novak found indubitable evidence of ovulation in 3 of his patients, and Elterich found that pregnancy had occurred in 30 patients of 12 years and under. This fact, together with the report that no lesion manifested itself in later life, is strong suggestive evidence that the condition is a premature development of a normal process.

The writer describes the cases of 5 girls and 2 boys with sexual precocity of the "constitutional" type, and gives their hormone output. The girls were aged

to be thought of when a case of precocious puberty presents itself; and yet this variety is far less common than the constitutional, in which an otherwise perfectly normal puberty mechanism is released abnormally early. There are wide normal variations as to the age of puberty, anything between 9 and 17 representing the usual range. If 9, why not occasionally 8 or 7, or 3 or 2, in of course tremendously diminishing proportion.

In cases of this type, no tumor is demonstrable in the ovary or in any other endocrine gland, nor does any develop when such patients are followed over many years, as has often been done. I have thus followed quite a group of these patients for as much as 20 years. Only recently one of these, who began to menstruate at the age of 5, has given birth to her first baby. It was only by the grace of God that she did not have this baby at about that age or shortly thereafter, as she could have done had she been inseminated. Lena Medina, the youngest mother in the world, with the achievement of a baby at the age of approximately 5½ years, was not so fortunate, even though she achieved the front pages in both the lay and medical press of the day.

The cases of granulosa cell precocious puberty are characterized by precocious menstruation, but always of the purely estrogen-induced type, and never accompanied by ovulation. Such patients, therefore, do not conceive if inseminated, and this is the crucial physiological difference between these two types of precocious puberty. Yerena acted wisely and conservatively in abstaining from exploratory operation, since careful pelvic examination showed no suggestion of ovarian enlargement. Theoretically it would be possible that a granulosa cell tumor of subclinical size might be present, but the chances of this are very slight, and the patient would be subjected to no hazard by withholding operation, though periodic examinations through subsequent years are always advisable. If a definite enlargement of one of the ovaries is found, exploratory operation is justified, but my own experience in cases of this type has taught me that even then one often finds no tumor, but a simple cystic enlargement or a small follicular cyst.

There are still other types of precocious puberty, all rare. For example, an adrenocortical type, due to a tumor of the adrenal cortex, can occur, but it is usually distinguishable from the above 2 types by simple clinical study. In this variety precocious menstruation does not usually accompany the precocious body symptoms, and these are characteristically of heterosexual type. The abnormal growth of hair does not occur only on the genitals and in the axillae, but also on the face, extremities and often the chest and back. The clitoris is also enlarged, which is never the case in the constitutional and granulosa cell varieties. —Ed.)

TRANSFUSION OF MALE BLOOD IN FUNCTIONAL METROPATHIA HEMORRHAGICA

U. MATERA

Argentina

The author states that the androgenic hormones and progesterone constitute the treatment of choice in cases of uterine functional bleeding. By this means, the endometrium returns to its normal cyclical changes, whereas the endocrine balance is reestablished. It is true that simple curettage checks the bleeding, but it may also cause definite lesions in the endometrium of a woman in the reproductive phase of life. Hence, this procedure is a secondary plan of treat-

perhaps only microscopic granulosa cell tumor may be present, it would be hard to believe that such a small impalpable tumor would be responsible for the pronounced anatomical and physiological phenomena seen in such cases, and no such case, so far as I know, has ever been observed. The rational plan is to abstain from laparotomy, but of course to follow up with periodic subsequent examinations. I have followed this plan with at least 12 cases, and, although some of these patients have been thus followed for many years, no tumor has ever materialized, either in the ovaries or in any of the other endocrine glands. It is well to remember, as a further restraint on exploratory ardor, that cases of this constitutional type are numerically far more numerous than those due to granulosa cell tumors.

As to the cause of the constitutional variety we can only speculate, just as we speculate about such kindred phenomena as precocious dentition. For some unknown reason, probably of chromosomal or genotypic nature, a perfectly normal puberty mechanism is released abnormally early. For additional comments on this subject, especially as bearing on the distinction between the constitutional and granulosa cell types on the point of possibility of premature pregnancy, the reader is referred to the comment on the following abstract, by J. A. Yerena.—Ed.)

RARE CASE OF PRECOCIOUS PUBERTY

Jesus A. Yerena

Caracas, Venezuela

Obst. y Ginec. Latino-Amer., **5:** 171–177, 1947

Case report: An 8 year old girl developed menarche at the age of 4 months, and from then on continued to menstruate regularly every month (3/30). Lately she had a period of amenorrhea of $2\frac{1}{2}$ months, followed again by normal periods. At the age of 1 year her pubic hair developed simultaneously with the growth of her breasts. Axillary hair developed only 1 year ago. Examination revealed the pubic hair to be fully developed with normal external genitalia and intact hymen. Rectal examination revealed a uterus 2 inches in size and the adnexa entirely normal. The breasts were well developed but the axillary hair was scanty. Vaginal smears revealed estrogenic activity. The basal metabolism rate was plus 8. X-ray plates of the skull and sella turcica revealed no abnormality. No further exploration was performed.

The author discusses the etiology of this interesting case, analyzing the various causes of precocious puberty, such as: granulosa cell tumor, hyperfunction of the pineal gland, hypercorticoadrenalism, constitutional hypergenitalism, etc. Although the existence of a very small granulosa cell tumor could not be entirely discarded in this case, the author is inclined to believe that it is related to a precocious activity of the pituitary-ovarian system. This case is very similar to that of Lena Medina, of Peru, with the difference that the latter conceived.

(There would seem to be no doubt that the author is correct in his belief that his case is one of the so-called constitutional type of precocious puberty and not of the granulosa cell variety. Gynecologists read so much about the latter that this is the one which is apt first

these patients varied from 20 to 30 years. Methyltestosterone was employed daily during the 7–10 days preceding the menses, in the dosage of 10 mg., for a total of 3 consecutive cycles. In 90 per cent of the cases of dysmenorrhea, the results achieved were very good, and in the remaining 10 per cent the symptoms were only partially relieved. In the cases of premenstrual tension, better results were obtained: 40 per cent of the cases were greatly improved, and 60 per cent got fairly better.

According to the authors, this medication should be employed in the treatment of dysmenorrhea and premenstrual tension, conditions in which it seems to be very effective.

(There is much less enthusiasm for the endocrine treatment of primary dysmenorrhea than there was some years ago, but when it is to be tried, I believe that testosterone is more frequently useful than is progesterone, the employment of which for this indication was formerly rather popular. Not only have the results with the latter been unsatisfactory, but the rationale for its use has been made very shaky by the contradictory results as to the effects of this hormone upon the uterine musculature. When testosterone is resorted to, its use should be begun in the early part of the cycle, and not limited to the premenstrual period, as is so commonly done. Its action is anti-estrogenic, and estrogen is unquestionably the hormone responsible for uterine contractility. The best of all hormone treatments, though it is to be used only intermittently and not continuously, is the employment of large doses of estrogen, preferably orally, beginning very early in the cycle, usually the first day or second day of the menstrual period, and continued for approximately 2 weeks. One mg. doses of stilbestrol, or corresponding doses of other estrogens, can be employed. This dosage will inhibit ovulation, and it is now pretty well established that anovulatory cycles are characteristically painless. There are definite limitations of this plan, such as the undesirability of thus inhibiting ovulation too frequently when pregnancy is desired, the possibility of disturbing menstrual tempo, and the fact that the good results observed with the first cycle are apt to be much less striking with the second. But even an occasional surcease of severe dysmenorrhea confers a definite psychological uplift on the patient, convincing her that it is possible for her to menstruate without pain. And the psychological element can never be lost sight of in the management of dysmenorrhea, and in a large proportion it is the all-important one. Anyone who depends upon endocrines alone in the management of dysmenorrhea, with disregard of constitutional and psychological measures, falls far short of the mark and is quite sure to meet with more failures than successes.—Ed.)

ment since hormones have proved to be of help in the management of the disorder.　As a matter of fact, the author has resorted to the employment of biopsies in only very rare instances.　In most cases the clinical history alone proves to be sufficient in guiding the treatment.　Nevertheless, most patients do need curettage, not only because of the high cost of the hormonal products, but also the length of time required by treatment.　In order to avoid such hazards, male blood has been administered to patients with functional uterine bleeding at the Maternity Institute of the Hospital Iturrospe, of Santa Fé.

This plan of treatment has the following purposes:

(1) It inhibits estrogenic activity, which causes the glandular cystic hyperplasia.　This is accomplished through the antagonistic effect of the male hormone contained in the administered blood.

(2) It rapidly improves the general condition of the patient and helps reestablish the endocrine balance.

Very good results are reported by the author in 15 cases thus treated.　The bleeding stopped and the menstrual cycle returned to normal.　This quick, easy and economical procedure should therefore be employed whenever an adequate amount of hormones is not available.

(An obvious criticism to the rationale suggested by the author for this method of treatment is that very large amounts of blood would be required to supply the androgenic hormone in doses comparable to those so readily available in the commercial forms of testosterone propionate.　As to the value and need of the transfusion of either male or female blood per se in improving the general condition of patients with the more severe forms of functional uterine bleeding there is of course no question, and it is a common observation that in some unknown way it does at times have a more or less hemostatic action as well.

In the functional bleeding cases of early life, I agree with the author that curettage is most often unnecessary for diagnostic purposes, although in the occasional extreme case it may be indicated as the quickest way to stop the bleeding, at least temporarily, being in such cases combined with transfusion.　On the other hand, in the far more frequent bleeding of middle life, diagnostic curettage is very often indicated, and always before some decisive plan of treatment, such as hysterectomy or radiotherapy.　Here, as with all clinical problems, there is room for individualization.　If a woman gives a history of moderate menorrhagia extending over several years, with never a suggestion of intermenstrual bleeding, there is little reason for suspecting intrauterine malignancy, and little hazard in deferring curettage.　It need scarcely be added that any such expectant plan presupposes careful pelvic examination to eliminate any visible or palpable abnormality of the organs such as polyp or myoma.—Ed.)

DYSMENORRHEA AND METHYLTESTOSTERONE

R. Pineda and G. Campagnoli

Rosario, Argentina

The authors report the results obtained in 20 cases of primary dysmenorrhea and 15 of premenstrual tension treated by methyltestosterone.　The ages of

CONGENITAL ABSENCE OF VAGINA; TREATMENT AND AFTERCARE; REPORT OF CASE

R. J. CROSSEN

St. Louis

The author presents a case of congenital absence of the vagina corrected by the Wharton technic. Various other technics are discussed, including the Frank method whereby persistent pressure is applied to the area between the urethral meatus and rectum, and various operative methods. The earlier Baldwin technic, using a loop of gut, and that of Schubert, using a portion of rectum, were formidable procedures. Later, plastic methods which lessened the risk encouraged more frequent operative correction. Graves used 2 flaps from the labia minora and 2 from the thigh; Davis and Cron used just the labia minora, and Frank and Geist used a tubular pedicle flap from the thigh.

In 1938 Wharton reported a technic which, because of its simplicity and success, is now widely accepted and used. A transverse or semilunar incision is made in the vestibule where the vagina should be. A plane of cleavage is found and followed upward by blunt dissection. Bleeding points are caught and tied. A balsa wood form, in which a groove has been made to fit under the urethra, is covered with a condom and sterilized. The form is inserted and kept in place until the epithelium has grown in from the margins of the opening and covered the walls of the vagina. Wharton has improved on the technic by using Thiersch grafts sewed over the form.

Crossen's patient was planning to be married but had never menstruated. Examination revealed that there was no vaginal opening and on rectovaginal examination no pelvic structures could be felt.

At operation, a transverse incision was made where the vagina should have been and, with an assistant's finger in the rectum and a sound in the urethra, an area was opened by blunt dissection which admitted 3 fingers at the outside opening and the index and middle fingers to its full length. The Upjohn's fibrinfoam was placed in the cavity while the skin graft was taken from the inner aspect of the thigh. The graft was sewed over the balsa wood mold with the end of the mold at its midportion. The mold was introduced after removal of all fibrin gell and clots.

Postoperative care included keeping the patient absolutely quiet for 6 days with rectal routine and liquid diet. After 6 days she was started on mineral oil and allowed a bowel movement. On one occasion the patient passed the vaginal form into the bed pan while having a bowel movement. To prevent recurrence of this accident, a belt of the type used with a cup pessary was obtained and the thin rubber tubing was run through the screw eye in the end of the balsa wood form and then back up the belt. This worked perfectly, even when the patient was ambulatory.

VULVA AND VAGINA

VULVO-VAGINITIS IN CHILDREN

GLADYS M. SANDES

Practitioner, **159**: 484–485, 1947

While vulvo-vaginitis may be either primary (due to local causes) or secondary (as part of a generalized infection), the incidence is mostly due to the staphylococcus which has appeared first as a "boil" or similar lesion elsewhere in the body. The writer considers first the treatment of gonococcal vulvo-vaginitis. General hygiene and especially the prevention of spread of infection to others and re-infection of the child itself when cured is important. It is necessary to discover the causal factor, which is commonly one or both parents or another occupant of the household. Accidental infection is far the most common. Frequent sea baths prevent extreme local soreness, and bed rest is helpful in the acute stage. The administration of penicillin is more effective and less toxic than any of the sulfonamide drugs. Penicillin may be given in the form of vaginal pessaries (500 units each) inserted twice daily for 10 to 14 days, or intramuscularly, 20,000 units 3-hourly for 5 doses. During treatment the complement fixation test for gonorrhea must be watched and used as a test for cure. Tests should consist of the absence of clinical or pathological signs after a month's cessation of treatment and again 2 weeks later. Finally, a fortnight later, 0.25 cc. of gonococcal vaccine is injected overnight and tests taken the next day. If clear, the child is considered cured.

Vulvo-vaginitis is sometimes due to foreign bodies in the genital tract. When vulvo-vaginitis is considered secondary to infection elsewhere, treatment should be directed toward removal of the cause, e.g., tonsillectomy, treatment of urinary infections, etc., and it is usually sufficient to confine local treatment to frequent baths and the application of a soothing cream.

(Penicillin is now the sheet-anchor in the treatment of gonorrheal vulvovaginitis in most clinics, although it is usually employed by the subcutaneous rather than the vaginal route. Sulfa therapy is likewise effective. The estrogen therapy which marked such a sharp advance in the management of this formerly very intractable disease is still used in some clinics, and there can be no doubt of its great value, in spite of the fact that it has been in large measure superseded by penicillin. As a matter of fact, there is no reason why a double barrel therapeutic combination of the two plans should not be made use of. The complement fixation test as a criterion for cure would probably not in this country be considered as reliable as repeatedly negative cultures.—Ed.)

enema syringe for douching, and had mislaid the nozzle 9 months previously. The case is reported to show how long a foreign body of moderate size may be retained in the vagina without causing severe symptoms.

(All sorts of curious foreign bodies find their way into the vagina, with retention for sometimes many years. On 2 occasions within recent years I have, in patients who complained of profuse and foul vaginal discharge, fished out tampaxes which had been retained since the preceding menstruation. In postoperative check-up of recently operated patients, the gynecologist may occasionally retrieve vaginal packs which his interne forgot to take out during the patient's hospital stay. Lucky the gynecologist who can thus retrieve his own vaginal packs rather than have this done by some not-too-understanding competitor.

Long retained vaginal pessaries are the foreign bodies most likely to be found in the vagina. This was the condition in Grainger's case, with the added feature that the patient had hidden her fountain-syringe nozzle behind the pessary. I believe I have made previous mention in these columns of a recent case in which I removed one of the old-time glass-ball pessaries, the size of an orange, which had been retained for something like 13 years, and the removal of which was made difficult by the fact that an extremely marked vaginal stenosis had developed below the pessary as a result of senile vaginitis.—Ed.)

A COMPARATIVE STUDY OF VAGINAL AND CERVICAL CORNIFICATION IN HUMAN SUBJECTS

J. E. AYRE, P. M. CHEVALIER AND W. B. AYRE

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A study of vaginal and cervical smears was made in 125 patients. The smears covered all stages of the menstrual cycle and a large variety of age groups. Selective smears and scrapings were taken with a spatula from the lateral vaginal wall and the squamous margin of the squamo-columnar junction of the cervix. It is suggested that such smears should give more accurate results than a random aspiration with a curette.

It was found that 88.8 per cent of the cases showed the cervical cornification count to be higher than the vaginal cornification count, varying from 5 to 55 per cent. Equal cornification levels were observed in 7.2 per cent, and 4 per cent showed a higher count in the vaginal than in the cervical smear. (This varied from 5 to 10 per cent.) The over-all average difference between the cervical and vaginal cornification counts was 15.5 per cent.

It has been shown that the cornification count varies in individual patients with the physiological changes during the menstrual cycle, with a gradual rise during the follicular phase and a peak at the time of ovulation. Also, it has been shown that when estrogen is given to postmenopausal and castrate women the cornification level rises from a normal zero to levels seen in normal ovulatory cycles.

The authors suggest that the variability in vaginal and cervical cornification

Pyelograms were taken on the eleventh day to rule out abnormalities of the genito-urinary tract.

On the twelfth day the plug was removed and the vagina examined. A speculum was inserted all the way. The skin graft had taken over almost the entire area. By the fourteenth day the skin graft area was healed. At the patient's last visit, 10 months after her marriage, she stated that coitus was normal. The vagina admitted 2 fingers easily and the speculum could be introduced its full length and opened without causing any pain. 4 figures.

(The author reviews briefly the various procedures resorted to in cases of congenital absence of the vagina, but his preference for the Wharton operation will probably be endorsed by most gynecologists. Its technique is quite simple, the only hazard being trauma of the urinary canal or rectum, although this is practically eliminated by the simple precaution of a sound in the urethra and a finger in the rectum. The employment of skin grafts for the canal thus made gives quicker epithelization, but it has the disadvantage of usually necessitating the cooperation of a trained plastic surgeon.

I have found the various new types of hemostatic gauze, such as the one mentioned by Crossen, to be of much help in controlling the bleeding, usually not profuse, produced by dissection of the tunnel. The larger vessels can be tied, but even then there may be a troublesome ooze which is most easily controlled by the gauze. It is surprising how little discomfort the patient has from wearing the vaginal form. One of my patients went horseback riding within a few weeks of the operation and experienced no discomfort. After final removal of the form, unless the operation has been timed so as to be done shortly before marriage, I have been in the habit of advising a little "home work" for my patients, instructing them to insert the form overnight from time to time to ensure maintenance of a good canal.

There is no longer any justification for the Baldwin type of operation, although I believe that those of us who had occasion to do this in the old days will agree that it gave results not excelled by any other procedure. The operation, however, was one of great magnitude, and not without hazard, although the latter was probably less than with the Schubert type of operation, which was far less frequently done in this country than in the European clincs.—Ed.)

FOREIGN BODY IN THE VAGINA

G. J. GRAINGER

London

Brit. M. J., 2: 1011, 1947

This writer reports the case of a 60-year-old women who wore a 2½-inch watch-spring pessary for prolapse. The ring had not been changed for a year, and the patient complained of an unpleasant vaginal discharge and slight discomfort in the left iliac fossa, the latter having been present for 2 weeks.

The ring was removed with some difficulty, the author noting that it seemed to have an irregular bar fixed across its center. When it was removed, the "bar" was found to be the bone nozzle of an enema, which had become firmly jammed across the inner diameter of the pessary. The patient had used an

HIDRADENOMAS OF THE VULVA; REPORT OF FOUR CASES WITH AN EVALUATION OF THEM IN THE LIGHT OF ANALOGOUS BREAST LESIONS

J. A. CUNNINGHAM AND J. HARDY

Birmingham, Ala.

To date there are approximately 80 recorded cases of hidradenoma, the comparatively rare sweat gland tumor of the vulva. Despite the paucity of reported cases, these are the most common tumors found in the vulva. The authors found in their files during a 4-year period 5 vulval tumors, 4 of which were of sweat gland origin. Out of 64 vulval tumors in the Mayo Clinic files over a 33-year period, McDonald, Lovelady and Waugh found 32 adenocarcinomas of apocrine sweat gland origin. The highest incidence occurred between the ages of 40 and 50 years.

The tumors measure from 3 mm. to 5 cm. in diameter. When small, they usually present as cystic elevated nodules; when large, the overlying epidermis may ulcerate, with eventration of the cyst contents. The microscopic picture is usually that of an intracystic papillary tumor. Usually the tumors present no symptoms. As a rule, these lesions are clinically benign; only 3 of the 80 recorded cases have shown frank malignant characteristics.

The writers feel that these lesions are analogous to the intraductal tumors of the breast, basing their belief upon embryological considerations, parallelism of clinical behavior, and the striking morphologic similarity of the lesions.

In the fetus a milk line develops which extends from the axilla to the groin. In man, all but the pectoral mammae normally regress. Histologically, there is a massing of sweat glands along the milk line. Apocrine sweat glands persist in the axilla and vulva, it being generally conceded that they become modified in the mammary region to form the parenchymatous portion of the breast.

Clinically, both the vulval hidradenomas and the intraductal papillomas of the breast are relatively benign and slow-growing, but occasionally may present malignant characteristics. Both may exist for long periods of time asymptomatically, or they may produce a slight discharge. Local excision usually results in cure, but in the vulva and breast the prognosis depends largely on the histology of the tumor.

Morphologically, the usual cystic vulval hidradenoma is indistinguishable from the benign intraductal breast papilloma. The more malignant varieties of vulval hidradenomas ape in remarkable fashion the intraductal papillary adenocarcinomas of the breast.

Although in the literature only one case was found in which a breast carcinoma developed after excision of a vulval hidradenoma, and although this was probably coincidence, the authors think that a possible connection between these tumors is at least thought-provoking.

counts revealed in this study may indicate either: (1) a greater sensitivity of the cervical epithelium to estrogen; (2) a difference in local concentrations of estrogen with a higher concentration in the cervix; or (3) a combination of (1) and (2).

There are a number of observations which suggest that the cervix is particularly sensitive to estrogens. When carcinoma is produced in experimental animals by large doses of estrogens administered over a long period, it is usually localized to the cervical tissue. After the twentieth week of gestation, the fetal uterus enlarges in response to the growth-stimulating effects of estrogen. While the body enlarges only to a limited extent, the cervix becomes twice as large in relation to the uterine body. When the estrogen stimulus is presumably withdrawn after birth, the cervix becomes relatively smaller in relation to the uterine body.

The great frequency of chronic cervicitis in humans arouses speculation as to whether there may be some etiological relationship between this disorder and the findings reported herein. 1 figure.

(The authors have been ardent followers of the Papanicaloau method of vaginal smear study, not only for the investigation of functional disorders, but even more in the diagnosis of cancer. The present study is an interesting one in that it compares the estrogenic cornification effects in the cervical squamous epithelium with those in the vaginal mucosa. These two mucous membranes are directly continuous one with the other, and it would be strange if the cervical squamous epithelium did not participate in the hormonal response characterizing the vaginal mucosa. And yet there has been very little direct study of the cervical response, so that it is of interest to learn that the authors found it even more marked than the vaginal.

The method of superficial cervical scraping would seem to be much more valuable for a study of this sort than selective smears, and more practicable than actual biopsy. I am not sure that what the authors say about the comparative cervical and corporeal growth effects produced by estrogen experimentally or occurring in the course of normal pregnancy will be looked upon as happy examples of greater cervical effects. The same statement may be made concerning their suggestion that the great frequency of chronic cervicitis in women may indicate an endocrine factor.

To revert for a moment to the subject of surface scrapings of the cervix, it has always seemed to me that this simple procedure is of much more value than vaginal smears in the search for very early, perhaps preinvasive carcinoma in women whose cervices show no lesion, and in which the ordinary biopsy would be a rather random procedure. J. E. Ayre has suggested a narrow spatula for this purpose, but an ordinary scalpel seems to me even better, the squamous surface being thinly pared in the region of the external os. A slightly oozing surface is left, but this quickly epithelializes. The delicate parings are at once washed off the knife blade in a wide test-tube of absolute alcohol and ether. After centrifugalization the tiny bits of tissue can be run through like an ordinary section, hematoxylin and eosin staining giving excellent results. Considerable strips and tags of squamous epithelium are thus obtained, giving a far more comprehensive idea of the cervical epithelium than can be obtained from smears.

My own experience with this simple technique during the past year or so leads me to think it is the procedure of choice in many cases, and that it should be of value also in studying the endocrine effects upon the cervical epithelium. The latter consideration is of great practical value. I believe that many instances of the so-called basal hyperactivity which are being so much stressed as possible precursors of cancer are really to be explained by such endocrine effects and we are now collecting cervical scrapings with the idea of making such cyclical studies.—Ed.)

PELVIC CELLULITIS WITH PERICOLIC AND PERIRECTAL STRUCTURE DUE TO NICOLAS AND FAVRE DISEASE

J. L. BOVERI

Rosario, Argentina

Obst. y Ginec. Latino-Amer. **5**: 407–420, 1947

The author analyzes the different aspects of lymphogranulomatosis affecting the internal genitalia, colon and rectum. This constitutes a rather rare form of Nicolas-Favre's disease, and the case reported in this paper is the second one registered in the Argentine literature. The etiopathogenesis and symptomatology of the disease are described in detail. As to its treatment, proteintherapy, antigentherapy, sulfa drugs in large doses, lugol solution, etc., are mentioned by the author, all of which yield unsatisfactory results. If the lesions should reach the stage of rectal stenosis, no treatment will prove adequate but the one based upon the performance of an artificial anus (colostomy). Extensive surgical procedures, such as resection of the rectum, yield very poor results.

A case is reported in a 28-year-old female, in whom all the internal genitalia, pelvic cellular tissue, sigmoid, rectum and urinary tract were involved by the process. The Frei test was positive (1:1000). Blood tests for syphilis were negative. Patient was treated with sulfa drugs, proteins, tartaric compounds, potassium iodide, rest in bed, etc. After 3 months, her general condition and intestinal symptoms were greatly improved, though her parametrio-adnexal condition remained practically unaltered.

(No one interested in the study of eponymic designations of disease can afford to overlook South America, where this system, so much inveighed against by many in our own country, flourishes to a high degree. I wonder if any of our readers had ever heard of Nicolas-Favre disease. I rather doubt it, and I am sure that I had not, so perhaps we've learned something. Aside from this, Boveri shows us that lymphogranuloma is not always a disease affecting only the genital and rectal areas, but that it may in rare cases be a much more extensive and formidable process involving such organs as the colon and the urinary tract. It is to this group of cases that the designation of Nicolas-Favre disease is apparently applied.—Ed.)

REACTIONS OF THE VULVA TO SYSTEMIC DISEASES

J. PARKS AND SHIRLEY MARTIN

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Am. J. Obst. & Gynec., **55**: 117–132, 1948

Regional reactions of the vulva to a number of noninfectious systemic diseases may be explained by anatomic and metabolic factors peculiar to this area of the

Brief summaries of the 4 case reports presented in this paper are as follows:

Case 1. White female, aged 56. Red papillary mass noted on right labium minus during urologic examination. Mass had been present for several months, was entirely painless, caused slight spotting of garments. Following local excision, microscopic diagnosis was papillary hidradenocarcinoma, Grade II. Patient was last seen 3 years, 8 months later; she was well, without evidence of recurrence or extension.

Case 2. White female consulted dermatologist because of small mass on right labium minus. This was excised. Pathologic diagnosis was intracystic papillary hidradenoma. Patient has not been located for follow-up.

Case 3. White female, aged 30, was examined because of congenital dystrophy of bladder. Several small tumor masses were noted on each labium minus. A biopsy from one of these nodules on the right labium showed papillary hidradenoma. Patient refused further treatment and has not been located for follow-up.

Case 4. White female, aged 49, complained of small mass on right labium majus. Pathologic diagnosis was intracystic papillary hidradenoma. Patient is still well, with no evidence of recurrence or extension. 5 figures.

(Hidradenoma of the vulva is a relatively rare lesion, but certainly not nearly as rare as would be indicated by the number of published cases. It usually causes no worthwhile symptoms, and the lesion is usually an inconspicuous one, being thought to be a small sebaceous cyst or skin fibroma. Often it is removed merely as an incident to some vaginal plastic procedure. When examined microscopically, the pathologist not familiar with its histological characteristics will often throw a bombshell at the surgeon by reporting adenocarcinoma, and this mistake has been made many times. In one large and excellent clinic, as quoted by the authors, a series of 32 vulvar adenocarcinomas of sweat gland origin was reported, although a glance at the photomicrographs and histories will convince the reader that most of these are simple benign hidradenomas.

Primary adenocarcinoma of the vulva may occur, but it is exceedingly rare, far more so than hidradenoma. The authors, not without reason, compare the latter to the intracystic papillomatous growths of the breast. This, however, applies to its pattern and not to any great extent to its cellular characteristics. The authors state that 3 of 80 recorded cases have shown frank malignancy, but in a comparatively recent study of the problem based on 5 cases, we found only 1 such instance, that of Eichelberger (Novak and Stevenson, Am. J. Obst. & Gynec., *50:* 641, 1945). It is true that several such cases are mentioned, but if one tracks down the original publications, as we did, I believe that he would eliminate all except the one mentioned above. While some authors hold the view that all such tumors derive from the apocrine type of sweat gland, I do not believe that the evidence for this is conclusive, and in our own study there was at least some evidence to suggest that the merocrine type of sweat glands may also be the source.—Ed.)

Some of the commonest contributors to allergic dermatitis are phenolphthalein, impure soaps, rectal ointments, phenol-containing douching materials and underclothing. The first reaction on the vulva is edema and itching followed by secondary trauma from scratching. The labia become swollen, the sebaceous glands of the labia minora stand out in relief, there is puckering of hair follicles of the labia majora, and fissures form over the perineal body and in the labial folds. A careful history is essential in arriving at a diagnosis. 10 figures.

(This is a very provocative paper, dealing as it does with various causes of vulvar reactions which the gynecologist is not likely to think of. Diabetic vulvitis is a well-known entity, but not many would be familiar with the fact that a slowly developing uremia can produce a typical ulceration of the vulva, nor would one be likely to think of the blood diseases mentioned by the authors as possible causes. While vitamin B deficiencies are known to produce ulcerative skin lesions elsewhere, it is probable that this factor likewise is often overlooked in the evaluation of vulvar lesions. The possible role of vitamin A deficiency in the production of leukoplakia is to be borne in mind, but therapy based on this concept has not yet been employed in a sufficient number of cases to be certain of its value.—Ed.)

HIGH LYMPHADENECTOMY AND SYMPATHECTOMY IN CARCINOMA OF THE VULVA

E. M. ROBERTSON

Queen's University, Kingston, Ontario

A case of carcinoma of the vulva, for which wide vulvectomy, bilateral inguinal and pelvic lymphadenectomy and right lumbar lymphadenectomy and lumbar sympathectomy were performed, is presented. The reasons for these procedures and their methods of performance are discussed.

The patient, aged 37 years, was referred to the writer for a nonhealing ulcer of the vulva which had been recognizable for at least 1½ years. The carcinoma stretched from the clitoris to the perineum on the right side, and from the outer edge of the labium majus to the urethra and just inside the vagina. The right subinguinal lymph nodes were markedly enlarged and somewhat fixed.

Vulvectomy was performed on Feb. 21, 1947. The anterior edge of the incision on the right side passed medial to the insertion of the adductor longus muscle, and included removal of some of the fatty tissue emerging from the ischiorectal space. On both sides the fascia overlying the adductor muscles was laid bare, and the soft tissue within the area defined by the pubic rami was cleared away. Medially, the incision partially ringed the urethra and entered the vagina for about ½-inch. To cover the exposed area, the adjacent skin was cut in all directions and a large flap was cut from the thigh on the right side.

The first lymphadenectomy was performed 35 days later. The left side was done on March 28. An incision about 7 inches long was made from a point one

body surface. Because of its vascularity, abundant nerve supply, frequent trauma, constant contamination, warmth, moisture and variable histologic structure, the vulva frequently reflects deficiency diseases, metabolic disorders and allergic reactions. Since the gynecologist is often consulted concerning lesions of this area, an understanding of reactions of the vulva to systemic disease is of real clinical importance. The writers describe and illustrate some clinical points in identification of vulval lesions associated with systemic diseases.

Agranulocytosis, aplastic anemia and acute leukemia cause peripheral vascular changes which results in deep, punched-out, oval areas of vulval ulceration covered with a thin grayish membrane and surrounded by very little induration or redness. The sensitive epithelium of the vulva readily reflects the avitaminosis and disturbed metabolism associated with pernicious anemia.

A typical ulceration of the vulval epithelium occurs in patients with slowly developing uremia. The inner surfaces of the labia minora and the dependent parts of the labia majora show a superficial excoriative type of ulceration covered with a thin grayish membrane and surrounded by brownish encrusted crystals of urea and uric acid. Weight loss, tissue dehydration and avitaminosis contribute to these changes.

In diabetes mellitus, disturbances of cellular nutrition and vitamin deficiency favor vulval dermatitis. Vitamin deficiency causes edema and itching. The sugar-containing urine and sebaceous secretions present on the vulva create a culture media for fungi and bacteria. Treatment should include correction of the diabetes, plus supplemental vitamins (particularly B complex), reasonable cleanliness and local applications to combat surface infections.

Probably the most common vitamin deficiency influencing the skin of the vulva is that associated with the B factors. Lack of riboflavin favors Candida infections. Skin ulcerations secondary to pellagra are often infected with Vincent's organisms. When estrogens are given to patients with subclinical vitamin B deficiency, they may cause characteristic lesions. Metabolism of estrogens increases the need for vitamin B. Among the other vitamins, of particular interest to the gynecologist are studies indicating the possible influence of vitamin A deficiency in the development of chronic dermatitis of the vulva with kraurosis and leucoplakia. The clinical significance of achlorhydria and vitamins in relation to skin changes of the vulva requires further investigation. The spectacular therapeutic results sometimes obtained with dilute hydrochloric acid administration remain unexplained.

While the cause of chronic atrophic dermatitis of the vulva remains unknown, neurogenic, hormonal, nutritional deficiency and allergic theories imply a sub-epithelial beginning for the atrophic and hypertrophic changes characterizing the condition. The authors discuss chronic atrophic dermatitis with emphasis on the internal factors which may contribute to its etiology. Treatment of this condition has been directed at measures which reduce inflammation, alleviate pain, improve cell metabolism and remove permanently damaged tissues. Eradication of all foci of infection is strongly advised. Treatment with vitamins and estrogen frequently improves the skin, but should be used only in early stages of the disease and under careful clinical control.

as definitely superior in their results to the vulvectomy and superficial inguinal adenectomy formerly in general use. And yet in the past few years results quite comparable to those reported for the Basset procedure have been reported from one or two of our clinics after operations of far more restricted and in some cases apparently very inadequate extent. It will be of interest to know the final result in Robertson's case, in which the operation was quite recent. In juxtaposition, but with no intention of trying to prove anything, I have in mind an elderly woman whose cancer was extremely extensive, almost the whole vulva being replaced by a foul ulcerated mass. Only a simple vulvectomy, without adenectomy, was done, with purely palliative intentions. It is now nearly 4 years since operation, and as yet there is not the slightest sign of any local or pelvic recurrence. These surprising vagaries are of course encountered in all types of cancer, but one gets the impression that they are especially frequent with carcinoma of the vulva.—Ed.)

inch above and medial to the anterior superior iliac spine, curving down to cross the middle of Poupart's ligament and continuing in the line of the femoral vessels. Block dissection of the fat, nodes and areolar tissue was begun about 2 inches from the termination of the saphenous vein. The vein was followed, ligated and cut near its junction with the femoral vein. The fat and nodes were then dissected from the fascia of the anterior abdominal wall, and at the external abdominal ring the round ligament was tied and cut. The block of tissue was then dissected from all sides toward the fossa ovalis. The femoral sheath was then opened, and nodes lying medial to the vein were removed. The gland occupying the proximal end of the femoral canal was then removed also. The inguinal canal was then opened, and with adequate exposure, the intact peritoneal sac was gently stripped inward from the underlying iliac vessels and lymph nodes. The inguinal and iliac nodes were then removed.

The operations of right lumbar sympathectomy and lymphadenectomy of the right lumbar, pelvic and inguinal nodes were performed 4 days later.

In discussing these procedures, the author states that it seems logical, always assuming that there is some connection between distant thrombosis, widespread vascular spasm, and such surgical procedures, to perform lumbar sypathectomy before or at the time of pelvic operation, the primary effect of which is to produce vasomotor paralysis. The reactions of increased blood flow and inactivation of the sweat glands might be considered of great advantage in vulvectomy and groin dissections not directly connected with the prophylaxis of vascular injury and vasospasm, namely, the promotion of better healing of skin flaps through increased blood supply, reduction of moisture from sweating, lessening of concomitant skin infection and avoidance of postoperative fissure at the vaginal introitus.

The extension of the range of the right lymphadenectomy to include the lumbar nodes was undertaken partly because lumbar sympathectomy was going to be done, and partly because these nodes form the next stage after the iliac group in the natural spread of carcinoma. In this case the retroperitoneal approach to the sympathetic chain and lumbar glands was made through an incision starting midway between the last rib and the iliac crest and ending one inch medial to the lateral edge of the rectus muscle opposite the umbilicus. The technique of White and Smithwick was otherwise closely followed.

It was not without very careful consideration that the accepted limits of surgical treatment of vulvar carcinoma were exceeded in this case, but the youth of the patient, the large size and prolonged history of the growth, confidence in the safety of modern surgical procedures to avoid shock and infection, and confidence in concomitant sympathectomy to lessen the chance of thrombosis and embolism, all were strong impelling influences.

(I do not believe that many gynecologists will try to emulate the author of this paper in the unusual extent of the radical procedure he describes, nor do I think they will be convinced of the wisdom of adding to it the additional sympathectomy which was carried out, and the rationale for which does not seem altogether convincing. Due largely to the work of the late Dr. Taussig, radical operations of the so-called Basset type have been accepted

as definitely superior in their results to the vulvectomy and superficial inguinal adenectomy formerly in general use. And yet in the past few years results quite comparable to those reported for the Basset procedure have been reported from one or two of our clinics after operations of far more restricted and in some cases apparently very inadequate extent. It will be of interest to know the final result in Robertson's case, in which the operation was quite recent. In juxtaposition, but with no intention of trying to prove anything, I have in mind an elderly woman whose cancer was extremely extensive, almost the whole vulva being replaced by a foul ulcerated mass. Only a simple vulvectomy, without adenectomy, was done, with purely palliative intentions. It is now nearly 4 years since operation, and as yet there is not the slightest sign of any local or pelvic recurrence. These surprising vagaries are of course encountered in all types of cancer, but one gets the impression that they are especially frequent with carcinoma of the vulva.—Ed.)

THE UTERUS

CERVICITIS

W. N. Searle

The patient having cervicitis always complains of vaginal discharge. The causal factors for this condition listed by the author are: (1) *Childbirth,* with eversion of the lips produced by tearing of the cervix and exposure of the columnar cells of the endocervix to the acid vaginal secretion. Hypersecretion of the cervical glands follows and in time Nabothian follicles are produced. In this "chronic cervix" there is a predisposition to cervical carcinoma. (2) *Infection,* the most common infecting organisms being the gonococcus, the trichomona and the coccus. A red, weeping, more or less circular, columnar-celled erosion results around the external os. (3) *Endocrine dysfunction* may produce an erosion, but endocrine therapy is disappointing.

When the patient's history or gross appearance of the discharge suggests infection, search should be made for the gonococcus by a gram-stained slide taken from the endocervix. If possible, a urethral specimen should also be examined. The trichomonas is demonstrated by immediate microscopic examination of a saline-diluted drop. The author mentions that a gonococcal or trichomonal infection may have been superimposed on a chronic lacerated cervix.

Treatment of the "chronic cervix" should consist of hospitalization with dilatation of the cervix and a radical cauterization of the endocervix as well as the vaginal cervix. The most common complication is secondary hemorrhage caused by separation of the slough from 10 days to 3 weeks after operation. During convalescence and repair, daily packing with gauze soaked in paraffin and flavine, or twice daily douches with alum, are ordered. More radical surgery is occasionally indicated—trachelorrhaphy, amputation of the cervix or hysterectomy. Amputation of the cervix should be avoided if possible in young women for fear of subsequent miscarriage or stenosis.

In trichomonas infection, stovarsol tablets or "S.V.C." are indicated, 2 to be inserted as high as possible at night with lactic acid douche in the morning. Bicarbonate of soda douches may help as much and make the patient more comfortable. Treatment should be continued for 3 weeks and the patient seen again after several days without treatment. In cases of recurrence it is suggested that cauterization of the endocervix, followed by daily packing for a fortnight with paraffin and flavine, may help.

It may be best that the proved case of gonorrhea become the responsibility of the venereologist, and penicillin by injection is the staff of treatment.

Finally, the author discusses the simple erosion—whether congenital or endocrine, in child or adult, but not accompanied by the signs of a chronic cervicitis

or proved infection. The simple erosion responds to cauterization of the eroded area, which can be carried out by application of the silver stick at weekly intervals, with astringent douches between treatments.

(In listing the causes of cervicitis and erosion, the author includes endocrine dysfunction, but I wonder if this can be substantiated. There is no doubt that hypersecretion of the cervical glands can be thus produced, as under entirely normal conditions such a hypersecretion has been shown to occur at about the time of ovulation, as a result of the estrogen peak then reached. But this functional response is quite different from the definitely inflammatory lesion implied by cervicitis, and due to infection by any one of a group of organisms introduced into the genital canal or normally residing there.

The author appears to me to make of radial cauterization a more formidable procedure than it actually is. With most of us it is a simple office procedure, and I do not believe that many would feel it necessary to subject the patient to daily packing of gauze soaked in paraffin and flavine. Following cauterization a patient should be told that she will have a disagreeable discharge for 2 or 3 weeks, and that it may be associated with bleeding, though this is ordinarily scant. It is true, however, that in the occasional case bleeding may be profuse, requiring a vaginal pack. All in all, however, radial electrocauterization of the cervix has impressed me as one of the most useful and satisfactory procedures in gynecology, being especially indicated in cervices showing marked erosion, with sometimes considerable eversion and more or less hypertrophy. Examination of such a cervix several months later will often show a remarkable degree of transformation, the cervix appearing quite "clean" and free of erosion.

In the intracervical types of infection, with profuse mucopurulent discharge from the canal of a cervix which externally seems quite normal, cauterization has no place, for the cautery should not be employed within the canal, usually very narrow in such cases, because of the great hazard of producing stenosis. The latter group of cases constitutes the ideal indication for conization, with perhaps an occasional tracheloplasty of the Sturmdorf type. Gynecologists will of course differ somewhat in their preference for cauterization or conization. The chief postoperative hazard of both is stricture of the canal, though this can generally be avoided by proper technique. When it occurs it is likely to make the lot of the patient worse than before.

Finally, the last paragraph of the abstract evidently refers to the simple congenital erosion seen in either children or adults. It causes no symptoms, or at most a slight mucoid discharge, and it calls for no treatment.—Ed.)

A NONSURGICAL METHOD OF THERAPY FOR CHRONIC ENDOCERVICITIS

L. V. DILL

Gallinger Municipal Hospital, the George Washington School of Medicine, and the Georgetown University School of Medicine, Washington, D. C.

A group of 25 patients, 8 parous and 17 nulliparous, were treated with a combination of stilbestrol and sulfadiazine for chronic cervical infection. All but 3 had a presenting complaint of sterility. Two patients had had therapy to the cervix for over 5 years, including repeated cauterizations and local therapy.

Therapy was as follows: three days after the onset of a menstrual period, one milligram of stilbestrol was given daily by mouth for the next consecutive 15 days; at the same time sulfadiazine, one gram 3 times daily, was taken by mouth for 3 days, the dosage then being reduced to one-half gram 3 times daily for 7 days. The endocervical mucus was re-examined at the ovulatory phase of the succeeding cycle and, if necessary, treatment was repeated in the following month.

Improvement was determined by microscopic examination of the cervical mucus; when this was free of leucocytes and the viscosity approximated that of saliva the specimen was considered satisfactory. Of the 17 nulliparous patients treated, 14 were cured, 2 improved and in one no change occurred. Of the 8 parous patients, 7 were cured and one was improved.

The rationale of this type of therapy is the combination of estrogenic enhancement of resistance of the cervical mucosa with stimulation of overgrowth and the antibacterial effect of the sulfonamide drug.

(Penicillin and the sulfa drugs are our most potent agencies in the treatment of cervical infections, particularly those of gonorrheal origin and those in the acute stages. But this form of therapy in itself will not by any means cure all cases of cervical leucorrhea. It is possible that a combination of stilbestrol with sulfadiazine may be more frequently helpful than sulfa therapy alone, but it is difficult to believe that this would eradicate the deep-seated cervical infections, with glandular hyperactivity, which are so often seen in the intracervical types of cervicitis. In these the cervix may show no external erosion and may, indeed, be quite normal in appearance, so that nothing is to be gained by the simple radial electro-cauterization which usually is so strikingly effective in restoring to normal even an extensively eroded, spongy and hypertrophic cervix. In the intracervical varieties, in which a profuse mucopurulent discharge is given off from the canal of an externally normal appearing cervix, conization and at times the Sturmdorf type of tracheloplasty are the usual methods of choice. If in such cases the method of treatment recommended by Dill is found by further trial by others to be effective, it will be a *worthwhile addition.—Ed.*)

A NEW ENDOMETRIAL BIOPSY CURETTE

T. R. HANNON

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The endometrial biopsy curette described in this paper has, in the author's hands, eliminated the undesirable features of the suction curette, and the author believes it to be superior to other curettes.

The curette consists of a head which contains a steel cutting edge similar to the sharp loop curette. Just below and distal to this cutting edge is a hollow trap to retain the detached endometrium. The size of the cutting head gives a fairly satisfactory sized piece of tissue with only one sweep of the instrument. The end of the shaft adjacent to the cutting head is of soft malleable brass which

can be molded to fit any type of contour. The larger four-sided handle makes for greater ease in handling the instrument. 1 figure.

(There are various types of endometrial biopsy curettes and punches, but taken as a group, the former seem to me preferable to the latter, simply because they yield more abundant tissues. The most common indication is to determine the condition of the endometrium premenstrually, in order to study the hormonal response of the latter, and most frequently to determine the occurrence or non-occurrence of ovulation. Instead of seeing only a tiny bit of tissue, it is just as easy, and more desirable, to curette away a good deal, as thus one gets a far more comprehensive idea of the endometrial pattern. My own preference, quite naturally, is for the Novak suction curette, which accomplishes just this purpose. Whether one uses electric suction, the water-pump, or the hand bulb, or no suction at all is a matter of individual preference, although I believe that the suction principle is a useful addition to the technique. I am sure, also, that others have found other types of instruments just as satisfactory.—Ed.)

ENDOMETRIOSIS OF THE INTESTINAL TRACT

M. R. SUTLER

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The increased recognition of endometriosis and its extragenital manifestations in the past 10 years has characterized it as a general medical problem. It has been estimated from comparative statistical reports that endometriosis exists in 10 to 22 per cent of all patients requiring gynecologic abdominal operations and in 8 to 15 per cent of all women during active menstrual life. Among 140,716 histologic diagnoses made by the pathology department of this university from 1934 to 1944, endometriosis was noted in 848 patients (0.60 per cent).

The intestinal tract is a highly significant extragenital location for endometriosis. In the material studied by the writer this site was involved in 35 patients (4.13 per cent); the appendix in 25 (2.95 per cent), the ileum in one (0.12 per cent), and the rectosigmoid in 9 (1.06 per cent).

Involvement of the small intestine is usually indicated by adhesions of the terminal ileum to pelvic structures with endometriosis of the loops of small bowel. Extramural invasion occasionally develops to the point of obstruction. Resection and anastomosis often effect immediate relief, but verification by frozen section and castration are necessary if recurrence is to be obviated.

Appendical endometriosis is nearly always coincidental with more prominent adnexal disease. Of the 20 extramural specimens in this study, however, 10 were unaccompanied by other abnormal tissue. Of the intramural cases, 3 had coexistent right ovarian endometriosis and 2 were without associated endometriosis.

It is estimated that 2 to 4 per cent of all women during active menstrual life have rectosigmoid invasion of some degree. These lesions may become of major diagnostic and therapeutic significance, for occasionally malignant disease is

closely simulated. Of the 9 patients in this study, 3 were preoperatively considered to have carcinoma and were partially or completely treated on that basis. The writer calls attention to the roentgenographic pattern in one of these cases which was so typical of that seen in carcinoma of the sigmoid colon.

Endometriosis simulates malignancy, not infrequently coexists with malignancy, and the ectopic cells themselves may undergo malignant degeneration. Although in this series 2 patients appeared to have adenocarcinoma arising in ectopic endometrium, evidence excluding coexistence was not convincing. 2 figures.

(More and more cases are being reported of endometriosis involving the intestinal tract. For example, a report of 16 cases of endometriosis causing intestinal obstruction has appeared as this goes to press, and it will be abstracted in a later number of the Survey. (McGuff, Dockerty, Waugh and Randall, Surg., Gynec. and Obst., 86: 273, 1948.) It is not surprising to find infiltration of the rectum, sigmoid or other parts of the bowel in cases of extensive pelvic endometriosis. The rectum, for example, may show such massive infiltration that it looks and feels for all the world like an advanced carcinoma. Where the pelvic organs are the seat of advanced endometriosis, the nature of the rectal involvement can be almost assumed, though one usually prefers to reinforce this impression with biopsy.

The treatment of these may in large measure disregard any attack upon the bowel lesion, unless there is actual obstruction. No one now would undertake the extensive and very difficult resections which at one time were advocated in such cases, including also those of so-called "adenomyoma of the rectovaginal septum." If all ovarian tissue is removed, the bowel lesion will practically always take care of itself by retrogressing.

A more interesting though less common type of intestinal endometriosis is that which is found in the absence of any such disease in the ovaries or other genital structures. I have within the past 2 years seen 2 such cases, 1 involving the rectosigmoid and the other the ileum. In the latter a dense annular lesion was noted accidentally in the course of operation for a large myoma, there being no suggestion of pelvic endometriosis. The intestinal lesion was thought to be an annular carcinoma and this opinion was concurred in by the roentgenologists. A resection and anastomosis were done, but microscopic examination showed endometriosis and not carcinoma.

There is something in the milieu of the true pelvis which appears to be essential for the development of endometriosis, and it is presumably because the small bowel and appendix, for example, are frequently pelvic organs that they may be the seat of endometriosis.—Ed.)

ENDOMETRIOSIS OF THE APPENDIX

Lucas M. Machado

Belo Horizonte, Brazil

The author reports a case of endometriosis of the appendix in a 36-year-old female, who had already been submitted to an operation for endometriosis of the inguinal region, about 9 years previous. Under the diagnosis of chronic appendicitis and fixed retroverted uterus, the patient was operated upon. The ovaries

were bound down by adhesions to the posterior surface of the uterus and sigmoid, and both presented small chocolate-colored cysts on the surface. The appendix was located in the pelvic cavity, with no connection whatsoever with the adnexa, and revealed a small, round nodule on its extremity. Pathological examination showed typical endometriosis of the appendix. The author discusses the histogenesis of this condition, and is inclined to believe that in this particular case the endometrium in the appendix originated from the spilling of the ovarian chocolate cyst contents. This case constitutes the first one of endometriosis of the appendix observed by the author among material comprising 45 instances of ectopic endometrium.

(Endometriosis of the appendix is not common, but is quite sure to be encountered from time to time in all laboratories where a large amount of gynecological pathological material is examined. Over the years I have encountered quite a number of instances, usually of course in association with ovarian endometriosis. The appendiceal endometrium is always seen on the peritoneal surface, but may at times involve the musculature as well. As a matter of fact ectopic endometrium may involve any structure in the true pelvis, that is, below the level of the ileopectineal line. The appendix is among these structures, since it is often a pelvic organ. There is something in the pelvic milieu, presumably celomic tissue with the potentiality to form endometrium, which is sometimes expressed in the formation of actual ectopic endometrium. This factor, whatever it is, is not present in the general peritoneal cavity. Even in the most extensive cases of pelvic endometriosis, one does not find endometrial islands above the pelvic brim.—Ed.)

CANCER: EVOLUTIONARY REVERSION IN CELL METABOLISM

W. B. Ayre and J. E. Ayre

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It is proposed by the authors that cancer is essentially a reversion in cell evolution resulting from an abortive attempt of the regenerating cell to adapt itself to an environment that is deficient in one or more of the elements essential for the formation of the enzyme pattern it requires to become a fully differentiated specialized cell. Recent studies have revealed a marked similarity in the enzyme patterns of embryonic and malignant cells. There is also evidence to suggest that a chronic low grade tissue vitamin deficiency which results in impaired function of the normal adult cell shifts the metabolic balance in favor of the growth and development of a cell with an embryonic cell enzyme pattern. When the cell environment is marginally deficient, the low concentration of one or more of the essential elements may not permit synthesis of the adult cell enzyme systems and yet may be entirely adequate for the synthesis of the enzyme pattern of an embryonic cell. It is suggested that when chronic nutritional deficiency and continuous forced local tissue growth obtain over a long period, the newly formed

regenerating cells will by gradual stages revert morphologically as well as enzymatically, and finally assume all of the behavior characteristics of the primitive embryonic cell.

In studies on uterine cervical cancer, three essentials in carcinogenesis have been postulated, and these might be adaptable to cancer in general. These three essentials are as follows:

1. The existence of a focus of chronic irritation where cell division is a part of the process of regeneration and repair and must continue as best it can in spite of the nutritional environment.

2. A tissue vitamin deficiency that alters the cell environment, making it impossible for the new cell formed in the process of regeneration to complete the enzyme equipment of a fully differentiated cell, but at the same time adequately fulfilling all of the metabolic requirements of an embryonic cell.

3. A hormonal factor which acts upon the cell which has assumed its embryonic character enzymatically and morphologically, and stimulates its further development, growth and invasiveness.

The authors feel that the hormonal effect operates by altering the permeability of the cell membrane. Sudden increases in the hormonal content of the body tissues may make available to the neoplastic cell which has been dormant the materials which are essential for the operation of its enzymatic systems, and its growth potencies manifest themselves. In general, it may be stated that invasion results from a complete breakdown in the mechanism for control of growth potencies in the cell. The cytoplasm of the cell contains a "prepotent" group of enzymes which rapidly utilize energy materials; thus, little of this energy material is available for the nuclear enzyme systems. This then is also a growth controlling factor. If there is chronic subnutrition of the cytoplasm, changes in its enzymatic systems may make available more energy material to the nucleus, thus promoting growth for growth, and regeneration is controlled by the nucleus. This, then, plus the hormonal effect on the cell membrane seem to be factors in determining the invasiveness of the cell.

(The authors, and especially one of them (J. E.) have been closely identified with work in the field of vaginal cytology, especially as applied to cancer diagnosis, and in this field they have done good work and shown a greater degree of conservatism than have some of the other enthusiasts for the method. On the other hand, when they undertake to tackle some of the basic problems of cancer histogenesis, as they do in this paper, their showing is far less impressive. This paper impresses me, at least, as based on a number of pure hypotheses, which will have to be supported by far more substantial evidence than anyone has been able to adduce before they can merit serious consideration, much less acceptance.

The Ayres lay down three essentials for carcinogenesis and I do not believe that any one of them can be considered as established. While the role of chronic irritation is thought to be of important predisposing importance in some cases, in others it appears to play no part whatsoever. Every gynecological pathologist must have been impressed with the fact that not a few cases of cancer, in these days of intensive search for early lesions, are found in cervices which otherwise are entirely normal and free of chronic infection. As regards carcinoma of the endometrium, no one would maintain that chronic infection plays any causative role, although it is possible that in some cases, especially those of postmenopausal type, hormonal irritation of the endometrium by postmenopausal estrogen might be of some

predisposing importance. The role of vitamin deficiency and enzymes may be of some importance, but neither the authors nor any one else has thrown any impressive light on carcinogenesis through evidence in this field.

A simplified concept of cancer, which, so far as I can see, squares quite well with the evidence now available in the whole field of cancer research, is that there are 2 important factors involved. One of them is some unknown, and certainly sometimes inherited susceptibility of which we as yet know little. However, in some individuals this predisposition is so powerful that cancer is quite sure to occur, even in the entire absence of any such factor as chronic irritation. When this susceptibility is of lower degree, it may require this plus an extrinsic irritative factor to bring about cancer and this irritative factor may be traumatic, inflammatory, chemical or hormonal. Finally, in other individuals there is so little susceptibility of the genotypic variety that cancer will not develop, no matter how much and how prolonged an irritative factor may be. Whatever the mechanism, it is now accepted that the cancer cell is not a new cell, but that it represents a normal body cell which, whether by "somatic mutation" or otherwise, undergoes that irreversible change which converts it into the killer cell of cancer. But the nature of this intracellular change is still an enigma, in spite of the work of innumerable cancer students in the laboratories of all countries.—Ed.)

CARCINOMA OF THE CORPUS UTERI

P. H. OOSTERHAGEN

Pretoria

At the beginning of this discussion on corpus carcinoma, the writer considers several factors which may distort a given case. One of these is the patient's ignorance and failure to regard any abnormal bleeding or discharge as requiring immediate investigation. Another stumbling-block is the undue stress textbooks lay on the age incidence of corpus carcinoma, so that doctors are inclined to omit its possibility in cases of abnormal bleeding under 40.

It is very suggestive that continuous estrogenic stimulation may be an etiological factor. Adenocarcinoma of the uterus, associated with granulosa-cell tumor of the ovary, appears too frequently to be a coincidence. It is well to bear this possibility in mind when using estrogens for menopausal symptoms.

Two types of corpus carcinoma are recognized. Adenocarcinoma is the commonest type, and appears in 2 varieties: the diffuse type and the circumscribed type. In the last group must be included carcinoma beginning as a localized polypoid growth; unless curettage is done thoroughly, it is conceivable that this may be missed. The second type of corpus carcinoma, adenoacanthoma, consists of a mixture of squamous and glandular epithelium. It presents a lower grade of malignancy.

The first, most constant sign is hemorrhage; in a small group of cases there is only a serous, foul-smelling discharge. Diagnostic curettage and biopsy of the curettements are the surest methods to obtain an early positive diagnosis. Al-

though there may be a polyp to account for the hemorrhage, it is safest to do a curettage to rule out coexisting carcinoma. In expert hands, vaginal smears done routinely are of great value. The writer discusses the differential diagnosis.

Treatment with panhysterectomy alone yields a 60 per cent 5-year survival rate. Irradiation plus radium only is reserved for operable cases in which some contraindication to surgery is present. X-ray irradiation alone is not dependable. Combined preoperative irradiation and hysterectomy 4 to 6 weeks later gives the best results, with a 70 per cent 5-year survival rate. The average dose of radium is 2,400–3,400 mg. hrs., given every 10 days. Apparently, postoperative irradiation does not make much difference, provided operation is properly done.

(This paper adds nothing new, but it presents a satisfactory brief review of the subject.—Ed.)

CERVICAL CANCER IN YOUNG GIRLS

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Am. J. Obst. & Gynec., **54**: 982–986, 1947

Two cases of cervical carcinoma occurring in girls aged 12 and 19 years, respectively, are presented in this paper. The first patient, aged 12, was admitted to the hospital because of persistent leucorrhea of several months' duration. Biopsy of a large, polypoid, hemorrhagic, friable tumor on the anterior lip of the cervix revealed adenocarcinoma. Radium treatments were begun, a total of 3,000 milligram hours being given. Six months after her first admission, the patient was reported to be suffering from abdominal pain, vomiting, weight loss and lumps in the groin. She died 15 months after treatment was begun.

The second patient, aged 19 and nulliparous, was admitted complaining of vaginal discharge since the menarche at 9 years, and backache, weakness and nervousness of 3 months' duration. The menses had been profuse and prolonged. A soft polypoid mass was seen at the external os. Dilatation and curettage revealed epidermoid carcinoma of the cervix and chronic endometrial hyperplasia. Radical hysterectomy, bilateral salpingo-oophorectomy and appendectomy were performed. No residual tumor was found in the removed uterus and cervix. At 11 months postoperatively, the patient seemed completely well and showed no evidence of tumor recurrence.

The first case constitutes the seventh recorded case of cervical cancer in girls aged 12 years or under. The salient features of these cases are tabulated. The respective ages were 8 years, 7 years, 7 months, 6 months, 10 years, 22 months, and 12 years. Six cases showed adenocarcinoma; in one case the type was not

stated. Type of treatment included excision and cauterization, laparotomy, hysterectomy, x-ray and radium. Four patients died in 15 months or less; the remaining 3 patients were not followed.

In contrast to the preponderance of epidermoid cervical cancer in adult women, adenocarcinoma is the commonest type of cervical carcinoma in young girls. The conditions of unrest (higher estrogenic titers, menstrual cycles and pregnancies) which might conceivably favor neoplastic development in the squamous epithelium are lacking in prepubertal young girls.

The poor prognosis associated with cervical cancer in young girls in the past may be the result of inadequate treatment rather than any specific peculiarity of the disease. 2 figures.

(The remarkable fact about the cases of carcinoma of the cervix which have been reported in infants and young children is that all have been adenocarcinomas, this being true of all 7 of this group collected by Speert, including his Case I. His other patient had an epidermoid carcinoma, but she was 19, so that, unusual as cervical cancer is at this age, it does not compare in rarity with the adenocarcinoma group. The youngest case recorded appears to have been that of Palmer Findley, the age of this patient being 6 months. Another early case was that of Scheffey and Crawford, this patient being 22 months old. Through the kindness of Dr. Scheffey I had the opportunity of studying sections of this tumor, which was unquestionably an adenocarcinoma. Only very recently, Dr. Karl H. Wilson was good enough to send me sections of a cervical adenocarcinoma from a patient of 11 months on whom he had done a radical operation, and it is to be hoped that he will publish this case, on account of its interest and rarity.

It is not easy to offer a satisfactory explanation as to why these precocious cervical cancers so characteristically assume the adenocarcinomatous rather than the epidermoid form. The hypothesis suggested by Speert, ascribing an important influence to the lesser degree of unrest between the two types of cervical epithelium in the child as compared with the adult, as well as the absence of estrogenic hormone and the lesser thickness of the cervical squamous epithelium, may or may not play a part. Such factors play a predisposing role, a more important one being that the inborn susceptibility which appears to be essential to the development of cancer, but in varying degrees of strength, is in the occasional individual so overpowering that the disease breaks forth even in very early life. But no one knows anything as to the nature of this intrinsic susceptibility, and the answer to this cervical problem would throw much light on the whole cancer riddle.—Ed.)

PRECURSORS OF CORPUS CARCINOMA ESTROGENS AND ADENOMATOUS HYPERPLASIA

S. B. GUSBERG

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The author describes a pattern of adenomatous hyperplasia of the endometrium which bears a constant relation to estrogen stimulation in both benign and malignant tissues.

Data are presented concerning this endocrine-tumor relationship in 4 related

groups.   The first group discussed consists of those patients who develop a granulosa cell (or theca cell) tumor of the ovary.   If prolonged unopposed estrogen stimulation can produce endometrial carcinoma in individuals advanced in years, one would expect a significant percentage of patients with functioning ovarian tumors to respond with endometrial malignancy.   There have been increasing reports in the literature pointing to the fulfillment of this expectation. Hodgson, Dockerty and Mussey found that in a group of 38 postmenopausal patients with granulosa cell tumors, 21 per cent had accompanying corpus carcinoma.   Of 9 patients with functioning ovarian tumors studied by the writer, only one had associated endometrial carcinoma.   However, a striking degree of hyperplasia was noted in many.   One can place these hyperplastic endometria in a graded progression of activity which moves quite readily toward the malignant one.

The second category deals with hyperplasia of the endometrium following prolonged estrogen administration.   Twenty human endometria with advanced degrees of hyperplasia produced by prolonged estrogen administration have been studied.   In the more active-appearing tissues there were noted: crowding of the glands into a lawless pattern, heaping up of the epithelium into pseudostratified masses, at times accompanied by intraglandular budding, paler, sometimes eosinophilic staining epithelium, and occasionally syncitiumlike epithelial masses on the surface; these metaplastic areas were frequently focal.   This response was not found to be related to the quantity of estrogen administered, but rather to the persistent stimulus.

Thirdly, the author discusses adenocarcinoma of the human endometrium following prolonged estrogen administration.   Many experienced workers in the endocrine field have denied that estrogens possess carcinogenic properties in the human, and some have pointed to the widespread use of estrogens and the lack of precise evidence that malignancy has been produced by such administration.   The author suggests that it is important to bear in mind the probable importance of the genetic factor in creating tissue susceptibility to abnormal growth stimuli.   The case reports are presented of 5 patients who have developed adenocarcinoma of the corpus uteri following prolonged estrogen administration. One may dispute the relationship between the medication and the neoplasm in any case, in view of the well-known character of this tumor in remaining local for relatively long periods of time.   However, these histories are extremely suggestive of an etiologic relationship.   Three other corpus carcinomas and an ovarian adenocarcinoma whose development may have been accelerated by estrogen administration and their histologic pattern modified are described.

The writer has studied the endocrine background of patients with corpus carcinoma and has noted deviations suggesting abnormality of internal secretions: an increased incidence of infertility, delayed menopause and menopausal bleeding.   Also, it was noted that among women who had been treated radiotherapeutically for benign bleeding at the menopause, there were $3\frac{1}{2}$ times as many subsequent corpus carcinomas as would be expected in a similar sampling of the general population.

The well-defined histologic pattern recurring in these related groups of tissues discussed above suggests that endogenous or exogenous estrogens play a role in the development of corpus carcinoma. The author calls attention to the pattern of atypical (adenomatous) hyperplasia which is sometimes encountered in patients who have suffered repeated episodes of "functional bleeding". It is a papillary pattern of glandular activity of an identical nature to that which has been described in this paper as an end result of endogenous (functioning ovarian tumors) or exogenous (estrogen therapy) estrogen stimulation. These considerations suggest the probability that there does exist a type of endometrial hyperplasia which can progress to adenocarcinoma under suitable conditions. 34 figures.

(This is a valuable contribution, both in its discussion of the role of estrogens in relation to carcinogenesis, and in the description of various estrogen-induced endometrial patterns which may be and often are mistakenly diagnosed as adenocarcinoma. On this latter point, it covers about the same field as the very recent paper by Novak and Rutledge on Atypical Endometrial Hyperplasia Simulating Adenocarcinoma (Am. J. Obst. & Gynec., 55:46 (Jan.) 1948). Since modesty will probably inhibit the Editor from commenting on a paper of which he is one of the authors, when the abstract is later published in these pages, the paper of Gusberg gives an opportunity for a few reinforcing comments on the general subject.

As regards granulosa cell and thecomatous ovarian tumors, the common association of endometrial hyperplasia as a response to the estrogen production of such tumors is well-known. However, it must not be forgotten that this hyperplasia does not always assume the typical swiss-cheese pattern. It may be markedly adenomatous, with considerable gland atypia and epithelial proliferation, so that it may readily be mistaken for adenocarcinoma. As a matter of fact, just this mistake has been made in the interpretation of at least some of the published cases. On the other hand, unquestioned carcinoma has occurred in a still small but constantly growing number of cases.

Somewhat the same gradation of changes is noted from estrogen abuse in menopausal women. The fact that such estrogen stimulation may be followed by either cancer-like or genuinely cancerous changes in the endometrium should indicate the closest scrutiny of cases of supposed adenocarcinoma reported to follow excessive estrogen therapy, and the microscopic diagnosis in such cases should be established beyond question. No such report should omit good photomicrographs of the endometrial lesion, because in spite of the limitations of reproduced pictures, the reader can form at least some idea of the microscopic characteristics. In the only previous report that I know of as suggesting the development of endometrial cancer following estrogen therapy, that of Fremont-Smith, Meigs, Graham and Gilbert (J. A. M. A., 131: 805, 1946) it is unfortunate that no such illustrations were published.

Gusberg does present photomicrographs of 5 cases, but it is hazardous and probably unwise to comment on these, except to say that some of the pictures at least do not seem to be convincing of actual adenocarcinoma. I say this because they resemble certain endometrial pictures which we have encountered in our own work and which were described in the paper by Novak and Rutledge. On the other hand, such pictures as Gusberg's Figures 21 and 22 would be accepted by all.

The simple fact is that there is a certain group of cases, numerically not large, in which no pathologist can be sure as to whether they represent actual malignancy or whether they are really instances of unusual degrees of proliferative growth response to estrogen stimulation. Such cases should receive the benefits of cancer therapy. But there is also a larger group of atypical hyperplastic lesions in which one who is familiar with possible variations of the estrogen growth effect can exclude malignancy, and such cases do not require cancer treat-

ment, responding to the usual conservative plans of treatment, such as curettage and radio-therapeutic induction of the menopause.

Gusberg's paper includes a large number of excellent illustrations of these interesting atypical and borderline lesions.—Ed.)

THE USE OF MULTIPLE SOURCES OF RADIUM WITHIN THE UTERUS IN THE TREATMENT OF ENDOMETRIAL CANCER

A. N. Arneson, W. W. Stanbro and J. F. Nolan

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In about 1938 a planned method of treatment for corpus carcinoma was established at the Barnes Hospital and the Barnard Free Skin and Cancer Hospital. The method of radium treatment was changed from one employing intrauterine tandems to a technic using multiple capsules of radium packed individuallly into the uterine cavity to fill all available space. Radium is preceded by external x-ray application. Patients suited to hysterectomy are given preoperative x-ray and radium treatment.

Between 1936 and 1941, a total of 93 patients with corpus cancer were treated. During the transition to regular use of preoperative irradiation, a few selected patients were treated with hysterectomy alone. Of the 93 patients in the entire group, 45 per cent were considered inoperable because of advanced cancer or some constitutional disorder. The absolute 5-year survival rate for the 43 patients treated by irradiation alone is 27 per cent. For the 32 patients receiving preoperative x-rays and radium followed by hysterectomy the 5-year result is 68 per cent. Surgery alone was used in 18 cases, of whom 84 per cent are alive and well for the same period. The authors explain the unusually good results from hysterectomy alone on the basis of favorable clinical material. The absolute 5-year survival for the entire series of patients is 53 per cent.

The attempt is made to compare the relative effectiveness of treatment by intrauterine tandem of radium, and by the use of multiple capsules. Variation in survival rate is found with histologic type for treatment by radiation alone or in conjunction with hysterectomy. An improvement in clinical results was found for the use of multiple capsules. Variation in survival rate is found also with size of uterus. For treatment by radiation alone the results in uteri of small size were about equal for tandems and multiple capsules. However, among 4 patients with large uteri, there are no survivors for treatment by x-ray and radium tandem alone. The results from multiple capsules and hysterectomy appear essentially independent of uterine size.

Among patients treated by radiation alone, the use of intrauterine tandems resulted in survival of only 22 per cent, but 32 per cent of those irradiated with multiple capsules survived for 5 years.   For treatment by irradiation and hysterectomy the use of tandems resulted in survival of 54 per cent, while the value for multiple capsules was 79 per cent.

Among the 32 patients treated by hysterectomy after x-rays and radium, persistent tumor was identified in 47 per cent.   Of that group only 46 per cent survived for 5 years.   Among the patients in whom no tumor was identified the survival rate was 88 per cent.   Persistent tumor was found in 77 per cent of those irradiated by tandems, but in only 26 per cent of those in whom multiple capsules were used.

In view of the 88 per cent survival for patients without recognizable tumor in the uterus, it is noted again that no residual cancer was recognized in $\frac{3}{4}$ of specimens irradiated with multiple capsules.   Furthermore, 79 per cent of the 19 patients treated by multiple capsules and hysterectomy survived for 5 years. These patients were not selected clinical material.   Thus, there appears to be an improvement in clinical results for preoperative irradiation with multiple capsules of radium.

(Some of the best work in this country in the field of radiological therapy as applied to uterine cancer has come from Arneson and his associates.   While the present series is not impressively large, it has been carefully studied, and the authors are apparently justified in their conclusion that the employment of multiple sources of radium has an advantage over the intrauterine tandems in the treatment of corpus carcinoma.   It is of interest to note that they found a definite correlation between the finding of residual cancer after radiation and the final survival rate, and perhaps this is not surprising.   The much higher incidence of residual cancer (77 per cent) after tandem irradiation as compared to multiple capsules (26 per cent) appears very impressive.   The absolute 5-year survival rate of 53 per cent in a series which evidently included many advanced cases may be considered quite remarkable. —Ed.)

ADENOCARCINOMA IN A MYOMA

F. Defazio

Buenos Aires, Argentina

Case report: A 40 year old female presented a large pelvic tumor for 6 years prior to admission.   For the past 2 years she developed irregular genital bleeding. Examination revealed a huge tumor occupying the whole abdominal cavity, which was diagnosed as a multinodular myoma.   The patient was operated upon and a very large lobulated myoma was seen attached to the uterus by a broad pedicle.   The tumor was excised and the uterus and adnexa, due to their normal aspect, were preserved.   Pathological examination of the tumor revealed a some-

what necrotic area which proved to be an adenocarcinoma. Due to this unexpected result, a curettage was performed in order to study the endometrium of the uterine cavity. This was found to be entirely normal. The author thinks that in this case an island of ectopic endometrium enclosed within the myoma underwent malignant degeneration.

(As with so many papers dealing with pathological interpretations, it is very difficult to evaluate Defazio's report on the basis of the clinical data and the very poor photomicrographs which are included. I do not see how any pathologist could diagnose adenocarcinoma from such pictures, and in reporting such a freakish observation as a supposed primary adenocarcinoma developing in the substance of a myoma one would expect an author to present much more convincing clinical and photographic evidence than is embodied in the present report. That a metastatic deposit of adenocarcinoma might be seen in a myoma is conceivable, although even this would be exceedingly rare. Another theoretical possibility would be that the growth was an adenomyoma rather than a myoma, and that the island of supposed carcinoma might be a pseudomalignant hyperplastic endometrium, although the poor pictures make it appear to be chiefly stromal. On the whole I believe it unwise to get too much excited over this case in the absence of more impeccable evidence than is included in the author's report.—Ed.)

CANCER OF THE UTERINE CERVIX AND PREGNANCY

C. ZUCKERMANN

Mexico

Obst. y Ginec. Latino-Amer. 5: 225–235, 1947

Within 20 years the author has observed 7 cases of cancer of the cervix associated with pregnancy, among a material comprising 4000 cases of cervical cancer. Thus, the ratio is approximately of 1 cervical cancer with pregnancy to every 600 cases of this disease.

From a therapeutic standpoint, the author advises the following plan of treatment: complete surgical and radiotherapeutic treatment before the 6 months of gestation. The fetus ought to be considered as sacrificed. After the 6th month (fetus viable or approaching viability) the fetus should be saved and the patient treated either by surgery or by radiotherapy according to the case. In every case of cervical cancer associated with pregnancy, thorough preliminary medical studies ought to be undertaken before any surgical or radiotherapeutic measure is resorted to. Efforts should be dispended in order to help save both mother and fetus. Preference ought to be given to the mother only when she has a chance for cure or whenever the child will not definitely reach viability.

(The association of cervical cancer with pregnancy is relatively rare, much more so in most clinics than is indicated by its incidence in that of the author. The principles of treatment which he lays down are in general conformity with those followed in our own clinics. —Ed.)

A METHOD OF STUDY OF THE UTERINE CANAL

W. B. NORMENT

Greensboro, N. C.

The author discusses an aid to diagnosis of submucosal myomas, polyps and malignancy of the fundus uteri by hysterograms and by direct observation. It is stated that many patients are curetted repeatedly and submucosal myomas and polyps not diagnosed, the patients often being treated on an endocrine basis when uterine bleeding is due to mechanical causes.

In making the hysterogram, Rayopake, an opaque contrast medium containing an organic iodine compound and a polymetric form of alcohol, approaches an ideal medium. It may be injected directly into the uterine canal by a plastic cannula, or in those patients in whom bleeding continues and it is difficult to inject the Rayopake, then it is advisable to dilate the cervix and use an intra-uterine bag, into which the medium is injected. The plastic cannula is most often used; the writer discusses the advantages of this over the metal cannula.

The second method of study discussed in this paper is by direct and indirect vision, which is more important in detection of carcinoma of the fundus uteri. For this purpose, a transparent sheath encases an optical instrument. The tube is plastic, very transparent and highly polished on the exterior surface so that blood will not adhere to it. There is very little trauma on insertion of the plastic sheath; following which the optical instrument is inserted into the sheath and a thorough study is made of the entire uterine canal. 2 figures.

(The enthusiasts in the employment of hysterography have, it seems to me, met with a lukewarm reception among gynecologists in general as to the value of the method in the diagnosis of at least a number of conditions in which its diagnostic value has been urged. Personally I cannot conceive that it would be comparable in either simplicity or decisive-ness to curettage in the diagnosis of adenocarcinoma or endometrial polyps. As to submu-cous myomas which produce any worthwhile bulge above the surface, the experienced gynecologist accustomed to handle the curette for tactile purposes, much like an extended or elongated finger, will not be apt to overlook any such mound-like protrusion into the uterine lumen. This is certainly not to say that masses in the uterus cannot be overlooked, some-times glaringly and ludicrously. I know of two instances in which experienced gynecolo-gists, after evacuating the uterus in cases of supposed incomplete miscarriage, including the use of the curette, were chagrined by the fact that the patients shortly afterward had crampy pains and expelled fetuses of 2 or 2½ months. I recall how we teased one of these men by showing how nicely he had curetted the back of the embryo. In the same way one could obviously miss a small pedunculated submucous myoma. It cannot be denied that in the case of submucous myoma, a hysterosalpingogram might be of value, much more so than in the case of the more fragile lesions, such as adenocarcinoma or endometrial polyp.

As to visual inspection of the uterine cavity, various forms of hysteroscopes or utero-scopes have been described, but none has achieved any worthwhile usage. I recall that when Mikulicz, later the Geheimrath at the illfated University of Königsberg, was in Balti-more some 18 years ago he experimented with such an instrument upon the monkeys in the

laboratory of Dr. Carl G. Hartman of the Carnegie Institution. When he returned to Germany, he put the apparatus to clinical use and published one or two articles on the subject. But neither this instrument nor any other as yet devised has awakened any great interest among gynecologists in general. Let us hope that Dr. Norment's may meet with a warmer reception, although, without the slightest intention at disparagement, I am rather dubious.—Ed.)

UTERINE SARCOMATOUS ENDOMETRIOSIS

J. C. Ahumada, L. A. Arrighi and H. L. Guixa

Buenos Aires, Argentina

The authors report a case of sarcoma of the uterus arising in an island of endometriosis interna (adenomyosis), which constitutes a very rare condition. In fact, as sarcomatous endometriosis, there are only the cases reported by Robert Meyer and Philip and Huber. Momigliano also described a case of sarcomatous endocervicosis. Sarcomatous endometriosis arises in the stroma of the ectopic endometrium just as the epithelial portion of the latter may rarely undergo carcinomatous degeneration.

Case report. A 51-year-old female complained of pain and gradual increase in size of the abdomen during the 4 months prior to admission. Examination revealed ascites and a very large pelvic tumor. The patient was operated upon, and following the removal of a large amount of bloody peritoneal fluid, a large mass, partly necrotic, was seen to be attached by adhesions to the omentum and intestines. This rendered the visualization of the uterus and adnexa entirely impracticable. The whole mass was removed and the condition of the patient became gradually worse until death occurred 15 days later.

Pathological examination revealed a fibroblastic sarcoma developing in the stroma of islands of a pre-existing adenomyosis of the nodular variety. Due to its invasive tendency, the growth destroyed the myometrium and thereby reached the peritoneum. The endometrium of the uterine cavity showed no sign of sarcomatous degeneration of the stroma, nor any connection with the islands of endometriosis nor with the sarcomatous growth. Thus, a complete independence of the malignant neoplasm from the surface endometrium could be readily established.

(The senior author of this paper is one of the most distinguished of South American gynecologists and is the director of the University Clinic in Buenos Aires. Incidentally he is a member of the Board of Editors of the Survey. The case which he and his associates describe is an unusual one. There is no reason why sarcoma should not arise in the stroma of the ectopic islands of endometrium in adenomyosis just as it arises from the surface mucosa in the ordinary endometrial types of uterine sarcoma. And yet such cases have rarely been observed. This may be due to the fact that the finding of an early case, in which alone

such a histogenesis can be established, must be largely accidental. In advanced cases with extensive infiltration of the whole uterus, it would be difficult or impossible to distinguish such growths from endometrial sarcoma of surface origin.

The findings, as described by the authors, would seem to warrant their explanation of the origin of this tumor, especially as the surface endometrium was shown to be quite normal and intact. It must be remembered that even the histologically benign stroma is at times a very invasive tissue, penetrating deep into the uterine musculature without carrying with it any of the normal gland elements of the endometrium. This constitutes the so-called stromal adenomyosis, or, as some have called it, uterine stromatosis, a benign lesion. The stromal growth in these cases may even show a tendency to intravascular or endolymphatic penetration, as Henderson has described.

When the invasive stroma shows definite histological evidence of malignancy, it appears best to designate it simply as endometrial sarcoma rather than to apply to it any such designation as malignant stromatosis, as has been done by some.—Ed.)

THE ADNEXA

ADENOCARCINOMA ARISING IN AN ENDOMETRIAL CYST OF THE OVARY

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Adenocarcinoma arising in an endometrial cyst of the ovary is a rare condition; Sampson originally reported a case more than 22 years ago. Recently, Teilum and Novak have each described a case.

Sampson postulated rigid criteria for the proof of the endometrial origin of such a tumor. These were: (1) the coexistence of benign and malignant tissues in the same ovary which have the same histologic relationship to each other as in carcinoma of the body of the uterus; (2) the carcinoma must actually be seen arising in this tissue, and not invading it from some other source; (3) additional supportive evidence includes the attendance of tissue resembling endometrial stroma about characteristic epithelial glands and the finding of old rather than fresh hemorrhage.

The authors present the case of a 42-year-old woman who was first seen with an asymptomatic mass in the abdomen. An ovarian cyst had been removed 17 years previously, but its nature could not be determined. Examination revealed a large cystic mass, posterior to the uterus, fixed, non-tender and extending 3 fingerbreadths above the umbilicus. Operation revealed a large cyst the size of a 16 weeks' gestation, arising from the right ovary. It was chocolate in color. Loops of small bowel were adherent to the cyst, and the latter was adherent to the uterus. Supracervical hysterectomy and right salpingo-oöphorectomy were performed; the left tube and ovary were surgically absent.

The uterus contained 2 subserous leiomyomas. Microscopically, the endometrium was hyperplastic. There were scattered foci of adenomyosis, most of which were accompanied by a good amount of endometrial stroma. A uterine polyp proved to be composed of endometrial glands.

No endometrial inclusions were found in sections of the Fallopian tube.

Section of the cyst showed a thick fibrous wall with mononuclear cells, occasional plasma cells and a few polymorphonuclear cells. The inner lining was disorganized, but frequently a thin layer of cylindrical cells resembling those lining the endometrium could be made out. These occasionally dipped into the stroma in glandlike formation. The stroma here was denser and composed of thin spindle-shaped cells. Within the wall were also large macrophages containing blood pigments and small extravasations of blood. Sections from the friable portion of the cyst showed a necrotic stroma with masses of atypical cylin-

drical cells. These cells were heaped up and hyperchromatic, their nuclei vary-ing markedly in size and shape. Mitotic figures were present. Tumor cells did not break into the deeper layers of the cyst wall. The tumor cells often arranged themselves about lumina or along delicate stalks in glandlike or papillary for-mation. 4 figures.

(In one of his early papers on endometriosis Sampson suggested that at least some ovarian adenocarcinomas of the ovary might arise from aberrant ovarian endometrium, and at the time the idea seemed to many of us intriguing. With his usual investigative spirit he later described a considerable group of cases in which he thought that this method of origin was possible, highly probable, or convincing. Only his Case V would seem to be unimpeachable, though in a number of others there was a strong probability of the adenocarcinoma having arisen from an endometrial cyst. In addition to this case, the only others of the unques-tioned type, so far as I know, are those of Teilum, Kuzma (1 of the 2 cases reported by him), the one by the present authors, and the one reported by myself in the Rubin testimonial number of the Journal of Mt. Sinai Hospital 14: 529, 1947. In the case of my own the tumor could be shown to spring directly from the wall of an endometrial cyst. It was of interest to me that it was an adenoacanthoma, since the squamous metaplasia characterizing the latter is seen so frequently in the uterus (adenoacanthoma of uterus) and is so rare in the ordinary forms of ovarian adenocarcinoma. This makes evidence for the endometrial origin of my case of adenoacanthoma of the ovary all the more convincing.

It is my belief that not a few cases of adenocarcinoma of the ovary arise from ovarian endometrium, in spite of the paucity of proved cases. It is, however, only rarely that one sees this form of ovarian cancer in an early stage, and when it is more advanced, all evidence of its original endometrial origin would be blotted out.

Another reason for believing that such an origin of adenocarcinoma of the ovary may not be rare is the fact that the histological appearance and pattern of some ovarian cancers are exactly similar to endometrial cancer of the uterus. This fact adds to the frequent difficulty of deciding, in cases of combined ovarian and uterine adenocarcinoma, whether the uterine or the ovarian lesion is the primary one.—Ed.)

CARCINOMA OF THE PAROÖPHORON, INVADING THE RECTUM

A. L. ABEL

Proc. Roy. Soc. Med., 40: 834, 1947

A brief case summary is presented of a 66-year-old woman who complained of difficulty in defecation and some slight rectal incontinence for 3 months, with recent blood-stained vaginal discharge. Vaginal examination disclosed an ulcer crater in the posterior fornix, adherent to the rectum. Biopsy showed a papilli-form adenocarcinoma. Wertheim's panhysterectomy and abdomino-perineal resection of the rectum were performed. Histologic examination of the removed lower rectum with attached uterus, adnexa and vagina showed the general struc-ture of a malignant ovarian cystadenoma. The diagnosis was carcinoma of the paroöphoron, invading the rectum. 1 figure.

(I have never seen a case of carcinoma of the paroöphoron, although I have seen two instances of tumors arising near the ovary but not from it, and presenting a rather finely adenomatous pattern with chiefly cuboidal but somewhat polymorphic epithelium which suggested a mesonephric origin, probably from the paroöphoron. Both of these impressed me as benign, and this has been borne out by the fact that both patients have remained well after operation, one for 20 and the other for 3 years. The case reported by Abel was obviously malignant, and, if it actually did arise from the paroöphoron, as the author believes, exceedingly rare. I have not at this writing seen the one illustration, presumably a photomicrograph, accompanying his paper, although it is often difficult to form an adequate idea of the pathologic characteristics of tumors from published pictures. The only satisfactory way, and this is obviously impracticable in most cases, is for pathologists to sit down together and submit their slides to examination and discussion.—Ed.)

CONSIDERATIONS ON MEIGS' SYNDROME

A. Wolff Nette and J. Hamermesz

São Paulo, Brazil

The authors report a case of fibroma of the ovary associated with ascites and hydrothorax (Meigs' syndrome) and analyze the incidence, histogenesis, pathology and clinical picture of this condition. They finally arrive at the following conclusions: (a) Only the cases in which the ascites and hydrothorax disappear with the removal of the neoplasm can be classified as Meigs' syndrome. (b) This syndrome can be caused by fibromas, fibromyomas, thecomas, Brenner tumors and even, according to some authors, by ovarian cystadenomas and uterine fibromyomas. (c) In the majority of published cases, the main symptoms were dyspnea, abdominal tumor, cough and other cardiorespiratory symptoms. (d) This syndrome ought to be more frequently observed than the incidence reported in the literature. (e) Its pathogenesis has not yet been established. (f) The possibility of Meigs' syndrome ought to be borne in mind by the internist whenever he encounters a patient with hydrothorax and presenting no fever nor any cardiovascular or pulmonary causes.

(Not only fibromas of the ovary, but various other tumors, especially those of solid type, may produce this interesting syndrome, as enumerated by Nette and Hamermesz. Neither the mechanism of the ascites nor that of the hydrothorax is clearly understood, the latter especially being very much of a mystery. It is generally thought that some sort of transdiaphragmatic lymphatic diffusion or permeation of fluid takes place, but, although at least some experimental work has been done on the problem, the mechanism is still unknown.

The ascites found with some cases of solid nonmalignant tumors was in past years commonly thought to be due to transudation as a result of partial venous obstruction, due either to the weight of the tumor or to incomplete or partial torsion of the pedicle. This view appears to have been largely abandoned. Rubin, J. Novak and Squire, in the most recent comprehensive paper on the subject (Am. J. Obst. & Gynec., 48: 601, 1944) suggest that the abdominal fluid has its source in transudation from the tumor itself. One of our junior staff

members, Edmund R. Novak, has recently been studying the subject, and thus far at least is inclined to believe that this factor of transudation from the lymphatics and veins of the tumor may be the important one. This he believes is suggested by the frequent richness of superficial lymphatics and veins in the fibromas which have been studied.—Ed.)

GRANULOSA CELL TUMOR OF THE OVARY WITH ASCITES AND HYDROTHORAX (MEIGS' SYNDROME)

J. Botella Llusia and J. M. Bedoya

Madrid, Spain

The authors report a case of granulosa cell tumor in a 63-year-old female in menopause for the past 10 years. One year after the menopause had commenced, the patient developed irregular bleeding, which persisted up to the date of admission. Seven months following the menopause, she developed ascites, which required several paracenteses. On examination, ascites and hydrothorax (right side) were encountered, and the uterus was found to be diffusely enlarged, with a tumor attached to it. Suspecting an adenocarcinoma of the fundus, curettage was performed, which revealed endometrial hyperplasia. Under the impression of granulosa cell or thecoma of the ovary, laparotomy was performed. A large amount of peritoneal fluid was removed and a tumor was encountered in the left ovary. The uterus was very small in size, entirely free, and the right adnexa appeared normal. Left salpingo-oöphorectomy was performed, followed by uneventful recovery. Twenty days later the hydrothorax had already disappeared, whereas the ascites regressed only 2 months later. The pathological report revealed a granulosa cell tumor of the folliculoid variety.

The authors discuss the pathogenesis of the Meigs' syndrome, especially of the hydrothorax, which still remains unexplained.

(See comment on preceding abstract of paper by Nette and Hamermesz.—Ed.)

MALIGNANT DEGENERATION OF A CYSTIC TERATOMA OF THE OVARY

R. Mendes Oliveira and F. Muller

São Paulo, Brazil

The authors report a case of cystic teratoma of the ovary (dermoid cyst) showing carcinomatous changes. This case constitutes the second one observed at

the Department of Gynecology, University of São Paulo, and considering the whole group of cases of cystic teratoma of the ovary registered in that clinic, the percentage of malignant degeneration reaches 8.33 per cent. This figure is undoubtedly a very high one, being only exceeded by the one reported by Ssokolow (9%).

Pathologically, the case reported showed a pattern of adenocarcinoma in the malignant area, which is by far less common than malignant changes of the epidermoid carcinoma type.

Death occurred 3 months following removal of the ovarian tumor, the nature of which could not be established at the time of operation. It was large, yellowish in color and presented a nodulated surface, being entirely free and well encapsulated. Three months later the patient returned with great abdominal metastases, and in spite of the radiotherapeutic treatment resorted to, death occurred.

(One would have the suspicion that the primary tumor in this case was probably a teratoma rather than a simple dermoid, to use the 2 terms which are most commonly employed in this country. The authors describe it as a cystic teratoma or dermoid, characteristically benign. There is much doubt whether the term dermoid will be displaced by that of cystic teratoma, although the latter is technically correct. Moreover, to distinguish teratomas on the basis of whether they are solid or cystic is irrational, as there are other differences which are much more decisive. The dermoid is ordinarily made up of dominantly ectodermal elements, though mesodermal elements are also common. These elements, however, are likely to be of mature and well-differentiated character.

The teratoma, on the other hand, is usually a jumble of elements derived from all 3 of the fetal layers. What is more important, these are often of immature and embryonic type, so that even an expert histologist may have difficulty in identifying all of them. The malignant propensities of such embryonic structures are far greater than those of the more stable elements in the dermoid. I wonder, therefore, if the case reported by the authors could have been of this type, especially as adenocarcinoma arising in a simple dermoid rarely if ever occurs. Without having looked up the literature I do not recall ever having seen a report of such an observation, and have seen no such case personally. On the other hand, epidermoid carcinoma arising in a dermoid is not so uncommon, and we have had quite a number of instances of this type in our laboratory over the years.—Ed.)

HEMORRHAGES FROM THE CORPUS LUTEUM SIMULATING ACUTE APPENDICITIS

Lucas M. Machado

Belo Horizonte, Brazil

The author reports 4 cases of corpus luteum hemorrhage, all of which were preoperatively mistaken for acute appendicitis and operated upon as such. All of them referred to young women (22, 18, 15 and 17 years of age), and only one case revealed a cystic corpus luteum. The remaining ones presented apparently nor-

mal corpus luteum, though all of them bled freely into the pelvic cavity. Operative procedure consisted in partial oöphorectomy (2 cases) and oophorrhaphy (2 cases).

The frequence, symptomatology, diagnosis and operative treatment of such a condition are discussed by the author.

(The majority of such cases of abdominal hemorrhage of ovarian origin are mistaken for acute appendicitis, but when the bleeding is massive, ectopic pregnancy is apt to be suspected. This was the case in a patient of my own who was almost exsanguinated, the abdomen being filled with blood from a ruptured follicle. Much more frequently, however, the bleeding is of moderate and sometimes only slight amount.

Either a ruptured follicle or a corpus luteum may be the source of the bleeding, the latter being much more common. Bleeding characteristically does not occur at the time of ovulation, but a day or two later, in the stage of so-called vascularization. During this phase it is normal to find restricted bleeding into the corpus cavity, but occasionally the bleeding is excessive, converting the corpus into a so-called corpus luteum hematoma. It is easy to see, therefore, that in this stage bleeding may occasionally break through into the abdominal cavity.—Ed.)

SALPINGOMETER AND SELF-RETAINING CANNULA FOR TESTING TUBAL PATENCY

A. DECKER

New York, N. Y.

An apparatus has been devised which permits the safe introduction of small amounts of carbon dioxide by fingertip regulation. The instrument is equipped to measure the intra-abdominal negative pressure in cubic centimeters of water. The principle of the Foley catheter has been adapted to the cervical cannula employed. The cannula is introduced by means of a stylet which can be molded to any direction of the cervical canal. When properly introduced, the cannula remains in place and can be manipulated without the use of a tenaculum on the cervix.

Occasionally, tubal patency can be determined without resorting to positive intrauterine pressure. A negative intra-abdominal pressure of 15 to 30 cc. of water is created by assumption of the knee chest position. Subphrenic air will occasionally occur when a cervical cannula is introduced in this posture. Such an occurrence is indicative of normal, patent, nonspastic tubes. The ability to measure intra-abdominal negative pressure through the cervical cannula is positive proof of tubal patency and, at the same time, avoids the necessity of introducing intra-abdominal gas. The author now uses this procedure as a screening process before applying positive pressure.

The instrument is described and illustrated and the method of examination explained. 3 figures.

(In his paper the author states that there is need for a safe and convenient apparatus. Personally, I do not see how an apparatus could be much safer when properly employed than that of Rubin, as used by most of us, or more convenient.   Every year someone publishes a new and simplified technique of determining tubal patency, but I am frank to say that thus far none of these has appealed to me as a desirable substitute for the Rubin method, and this applies also to the apparatus described by Decker.   The negative intra-abdominal pressure plan which he advises is of interest, but I doubt whether many gynecologists would wish to bother about resorting to this as a screening process before applying positive pressure with carbon dioxide, especially as the latter is so simple and so readily measurable.—Ed.)

GRANULOSA-CELL TUMOUR OF OVARY AS ACUTE ABDOMINAL EMERGENCY

A. C. BREWER

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Brit. M. J., 1: 49, 1948

The case is reported of a 48-year-old woman who was admitted with a complaint of acute abdominal pain of some 12 hours' duration.   For the last 12 days she had had moderately severe diffuse lower abdominal pain which had become localized in the right iliac fossa, radiating into both loins.   There had been no vaginal bleeding since the menopause 4 years previously.

Examination revealed tenderness and muscle-guarding in the right iliac fossa. On vaginal examination there was tenderness in both fornices, more marked on the right.   Movement of the cervix caused pain.   The uterus was slightly increased in size.

At operation, about one pint of blood and clot was evacuated from the pelvis. An ovarian neoplasm of moderate size was removed, with blood clot extruding from 2 places in its capsule.   The uterus and left ovary appeared normal. Following right salpingo-oöphorectomy, the patient recovered uneventfully.

Pathologic examination showed a granulosa-cell tumor of the diffuse type. It had a dense fibrous capsule which was ruptured at 2 points.   Although hemorrhage into a granulosa-cell tumor of the ovary is common, the author can find no previous report of a case associated with so severe a degree of hemorrhage.

(Intra-abdominal hemorrhage can in the occasional case occur with almost any type of ovarian neoplasm, probably more frequently from the relatively thin walled cysts which may rupture, with occasional damage to blood vessels in the wall.   Granulosa cell tumors are often, especially when they reach large size, at least partly cystic, and, as the author states, hemorrhage into the tumor is not rare, and could conceivably break through into the abdominal cavity.   I do not recall, however, seeing any previous report of this occurrence.—Ed.)

FEMALE UROLOGY

THE DETAILED ANATOMY OF THE PARAURETHRAL DUCTS IN THE ADULT HUMAN FEMALE

J. W. HUFFMAN

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The material studied for this presentation consisted of serial sections and wax model reconstructions of adult human female urethras obtained from 11 necropsies. As a result of the study, a concept of the anatomy and histology of the paraurethral ducts is presented, and the role which the paraurethral ducts may play in the etiology of lesions of the urethra and anterior vaginal wall is discussed.

It was observed that the most distal paraurethral ducts open into the canal just within the meatus and extend outward from the urethral mucosa into the dense connective tissue which makes up the urethral wall. This wall is surrounded by and is an integral part of the dense connective tissue shelf (The urogenital diaphragm) lying beneath the vaginal mucosa.

In all specimens the greatest number of paraurethral ducts empty into the distal one-third of the urethral canal. (In 2 all duct orifices are in the distal centimeter of the urethral canal; in 6 the duct openings are limited to the distal 1.5 cm.; in 3 occasional tubules open into the urethral canal throughout most of its length.) There is a definite tendency for the mouths of the ducts to be in 4 groups, with 2 groups on each side, i.e., ventrolateral and dorsolateral groups on each side. Larger tubules are usually in the dorsolateral location. However, in addition to these major groups there are a considerable number of ducts opening into the lateral, the dorsal, and a few in the ventral urethral walls. After leaving the urethral canal, these tubules turn cephalad and promptly divide into small branches. These small branches wander outward in the lambia propia away from the urethral canal; they tend to pursue a course somewhat parallel with the urethra, and often extend cephalad for a considerable distance. It is not unusual for a single specimen to have a number of these ducts each of which with its branches and glands has an over-all length of from 0.7 to 1.2 cm.

More deeply within the urethra the number of paraurethral ducts opening into the urethral canal becomes less. However, in the more cephalic sections the dissemination of ducts, terminal tubules and glands away from the urethral canal and into the urethral wall is greater. At these levels the smaller branches of the larger ducts which have emptied into the more distal urethra terminate in multiple small budlike out-pocketings and tubular glands. These terminal structures are noted for the most part in the lateral and inferior urethral walls, but each specimen shows a considerable number of ducts and small tubules spreading

ventrolaterally and ventral to the urethral canal. This collection of ducts and glands forms a labyrinthlike mass dorsally and laterally which, when indurated by inflammation, produces the thickening so commonly felt after urethral infections.

In some specimens at higher levels the urethra is surrounded on all sides by many small tubular buds and glands which extend to the outermost limits of the connective tissue core making up the urethra itself. Dorsally, they may closely approach the vaginal mucosa. Lateralward, far from the meatus, at the cephalic end of the gland mass, and well away from the urethral canal, the terminal tubules and terminal glands frequently form thin semicircular masses which lie in the lines of stratification of the fibers of connective tissue encircling the urethra.

In the material studied, the presence of 2 large lateral ducts as described by Skene was the exception rather than the rule, and the widespread branching of the terminal divisions was more marked than Skene described. In but 2 of 11 specimens could 2 larger tubules, one on each side of the urethra, be followed for any distance. Except for their greater diameter and longer length, these tubules resembled the other paraurethral ducts seen in the same and other specimens; they were lined by the same type of epithelium and terminated in tubular glands just as the other ducts described. The least number of ducts found in any of the urethras was 6, the most 31.

Paraurethral glands have, in the past, occasionally been referred to as compound racemose or racemose structures. According to commonly accepted terminology "compound racemose" implies a number of branching ducts with numerous acini grouped about the termination of each duct, as in the major vestibular and parotid glands. The architectural pattern of the paraurethral glands does not correspond with this description. They are branched tubular glands, with straight or slightly curved branches, which empty into the paraurethral ducts. They are lined for the most part by columnar epithelium which is made up of cells varying from low columnar, approaching cuboidal, to moderately tall cylindrical cells. There are occasional nests of mucous secreting cells within this columnar epithelium. These cell nests have a definite secretory activity as demonstrated by mucicarmine stain. Not all branches of the ducts, however, terminate in glands; many end in small pockets, tiny dilated cystic spaces, and minute arborescent tubules which are lined by a pseudostratified columnar epithelium several times thicker than the lumen of the tubules itself. Infrequent intraepithelial glands of mucous secreting cells are found within this epithelium.

Most of the smaller and many of the larger branches of the paraurethral ducts are also lined by pseudostratified or true stratified columnar epithelium. Near their orifices the lining of the ducts becomes the same type as that of the urethra at that level, i.e., stratified squamous epithelium lines the ducts which empty nearest the meatus; the ducts which open into the midurethra are lined by transitional epithelium which frequently also comprises the urethral mucosa at that level.

Cystic dilatation of the ducts is apparently common, as it was seen in several

specimens; these dilatations occurred most often in the terminal portions of the tubular branches. One such cyst was larger than the adjacent urethra. These cysts are lined by flattened epithelium of the same type as that of the duct. Inflammatory reactions in and about the ducts and glands are common. Round cell and leucocyte infiltration has been observed beneath the epithelium, and minute localized abscesses and inflammatory destruction of the duct wall has been noted in several instances.

The author suggests that it would appear proper to enlarge Skene's description to include the many other large ducts and their glands which are present in most individuals and which are identical with the 2 which he described. Contrary to common assumptions, the prostatic homologue in the female is most often a widespread branching of ductal channels and glands surrounding the urethra to some extent on all sides. The marked variation in the extent of the paraurethral ducts in different individuals is also of interest.

The role of the paraurethral ducts in gonococcal infections is well understood. That these ducts may be involved in other types of urethritis is less commonly realized. Obstruction of the narrow outlet of infected paraurethral ducts is an important factor in the etiology of abscesses of the anterior vaginal wall. Paraurethral abscesses may also form in the urethral wall, rupture into the urethra, and eventually become urethral diverticulae. In view of the present study, it seems possible that retention cysts of the paraurethral glands and suburethral tissues might well cause cystlike tumors of the anterior vaginal wall.

In regard to primary carcinoma of the urethra, since the paraurethral structures contain intraepithelial mucous secreting glands and true branched tubular glands, it is understandable that adenocarcinomas may occasionally develop from them.

(The studies reported in this paper represent perhaps the best contribution of recent years in the field of female genital anatomy, and this paper should be read and studied by every gynecologist and obstetrician, especially since some of the observations have definite clinical connotations. Many readers will recall the splendid wax model reconstructions exhibited by the author at the last American Congress, and drawings of these models are included in the paper abstracted above. I am sure that a study of these will be a revelation to most of us, showing how naively simple and how glaringly incorrect had been the concepts of the paraurethral ducts which have come down to us from the time of Skene. Among other things, the author has found wide variability in the number as well as in the location of the ramifying ducts surrounding the urethral canal. A study of the paper and the illustrations will be much more instructive to the reader than would any scattered comment on my part as to the anatomical and clinical worth of this publication.—Ed.)

STRESS INCONTINENCE IN THE FEMALE

R. A. REIS AND E. J. DeCosta

Chicago, Ill.

The authors have reviewed the anatomy of the female bladder, urethra and related structures, and they point out that a great deal of the confusion which exists concerning this anatomy arises from multiple terminology plus the differences encountered at the dissection and operating tables. In brief, continence is preserved by a threefold mechanism: the internal sphincter composed of smooth muscles of the bladder neck, the longitudinal ridges of the urethra, and the external sphincter composed of the muscle fibers of the urogenital diaphragm.

The internal sphincter contracts if the bladder is distended, but contraction of the bladder brings about relaxation of the internal sphincter through the action of the trigone muscle, the longitudinal fibers of which pass through the internal meatus. This action is dependent upon the presacral (sympathetic) nerves. Ordinarily the external sphincter is relaxed, but it is brought into play by sudden rises in intra-abdominal and, hence, intracystic pressure.

Obstetric injury to the urethra and supporting structures is the commonest cause of stress incontinence. It is probable that the damage incident to parturition involves in varying degree, by stretching and tearing, all the structures associated with the bladder and urethra.

There are many generic types of operation which have been advocated and used in the treatment of stress incontinence. In analyzing the various procedures employed, one of several mechanical changes is made: (1) the urethra is lengthened or twisted; (2) the urethra and/or bladder is returned to its normal position behind the pubis; (3) the musculature of the bladder neck and/or urethra is plicated; or (4) a musculofascial sling is placed below the urethra. All of these procedures have in common the tightening of the fascial planes through which the urethra passes.

The authors have used the paraurethral fixation operation of Berkow to correct stress incontinence. The pubococcygeus muscles are approximated below the urethra and further support is given by uniting the two bulbocavernosus muscles as a second layer. By this procedure the urethra is advanced and slightly angulated, thereby narrowing the lumen, increasing its length and increasing the tension received from surrounding structures.

Paraurethral fixation was carried out by Reis and DeCosta in a series of 33 patients suffering from stress incontinence. Two failures were reported; one of these was in an 82-year-old nullipara who had had an anteroposterior suturing following total colpocleisis; the other was in a patient having a psychotic background. The only noteworthy complication was a change in the direction of the stream which necessitated tilting the body forward during micturition to avoid wetting.

(See comment following next abstract of paper by Moir.—Ed.)

URINARY INCONTINENCE FOLLOWING CHILDBIRTH, INCLUDING VESICO-VAGINAL FISTULAE

J. C. MOIR

University of Oxford

Edinburgh M. J., 54: 368–381, 1947

In discussing stress incontinence due to childbirth, the author emphasizes the importance of choosing the most applicable type of operation for correction of the cystocele, as the reported rate of failure of such operations is so high. The "sling" operation in one of its modifications is commonly the operation of choice. The writer compares the Aldridge, Studdiford and the Millin operations, pointing out the advantages and disadvantages of each, and concludes that for his own purposes he prefers the Aldridge operation. Using either the Aldridge or the Studdiford operation in a series of 14 patients there has been only one case of any serious recurrence of stress incontinence.

Concerning the vesico-vaginal fistula, Moir quotes Sir J. Y. Simpson who described it as "the most depressing and deplorable of all the infirmities of which woman is liable, a condition looked upon as beyond all relief and hope." Again the author emphasizes that the choice of operation is of paramount importance if a cure is to be effected. In general, he prefers the "saucerising" operation, without mobilization of the bladder. Suture tension is relieved by dividing the vaginal bands or ridges by an incision parallel to the suture line. The relaxation-incisions usually heal promptly by granulation. Exposure of the fistula may be improved by an episiotomy or by having the patient kneel on a low stool at the bottom of the operating table. The author does not believe that catgut should be used, but prefers nylon or silver wire, and the sutures are not removed in less than 20 days. A plain catheter is tied into the urethra and suction is maintained for at least 12 days.

Using the above outlined regime, Moir has succeeded in obtaining closure of the fistula in every case in a series of 40. Two cases required a second operation.

(It is difficult to believe that Moir recommends some type of "sling" operation, of the Aldridge or Studdiford types, in the ordinary case of stress incontinence associated with cystocele, as simpler types of operation of the general type recommended by Reis and De-Costa will correct the disorder in the great majority of cases. The latter authors, incidentally, present a good anatomical discussion as well as a brief review of the various procedures applicable to most cases of stress incontinence.

The more difficult and extensive procedures of the Goebel-Stoeckel, Aldridge and Studdiford types are in most cases reserved for the more intractable cases of stress incontinence, in which as a rule previous operations of simpler type have been unsuccessful. In this limited group the reported results have on the whole been gratifying.—Ed.)

URETEROVAGINAL FISTULA: REPAIR OF URETERAL DEFECT BY USE OF BLADDER FLAP

G. V. Caughlan

Council Bluffs, Iowa

The writer describes a method for repair of a ureteral defect. A 35-year-old woman complained of persistent dribbling of urination since the performance of a complete hysterectomy 4 months previously. She also complained of a dragging pain in the left kidney region.

Following examinations, the diagnosis of left ureterovaginal fistula secondary to hysterectomy was made.

At operation the left ureter was found to be dilated about twice the normal size with the distal end buried in a scar tissue mass. The ureter was divided as low down as possible and freed upward; it was about 4 cm. short of reaching the bladder. An incision was made in the vertex of the bladder wall 2 cm. in width and 5 cm. long, forming a tongue. This was laid back to form a new ureter, and stitched to the posterior wall of the ureter. A 12 F. soft rubber catheter was passed up the ureter to the kidney, and this was used to make a new tube of the bladder tongue, closure being made over this catheter with a double row of 00 chromic gut. The bladder was closed, a drain introduced to the anastomosis, and the wound closed.

Five years after operation, the patient has had no trouble, the urine is clear and there is no evidence of obstruction to the left kidney. 2 figures.

(This was a case of Mahomed going to the mountain instead of vice versa. Undue tension is always a hazard in any type of anastomosing operation, and in the case described by the author, where the ureter was much too short to reach the bladder, the expedient which he employed was an ingenious one, and was rewarded with success.—Ed.)

INTRAPERITONEAL RUPTURE OF THE URINARY BLADDER IN THE FEMALE: REPORT OF A CASE

C. D. Tool

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Rupture of the urinary bladder is usually intraperitoneal in men and extraperitoneal in women, due to anatomic differences in the location of the bladder. A review of the recent literature discloses only 5 cases of traumatic intraperitoneal

rupture of the bladder in nonpregnant women. In 3 of these, trauma was accompanied by fracture of the pelvis.

The writer reports the case of a 15-year-old girl who sustained a severe crushing injury in an automobile accident. She was critically ill from the time of admission until death which occurred 3½ days after the injury, and operative intervention was not possible at any time. At autopsy a compound fracture of the pelvis was revealed, together with a rent, 2 cm. in diameter, on the peritoneal surface of the urinary bladder. The opening on the pelvic peritoneal surface led to a surface wound of the vulva. The author suggests that it is probable that the urinary bladder was distended at the time of the injury. If a woman with a distended bladder suffers a severe crushing injury to the lower abdomen, especially if accompanied by fracture of the pelvis, rupture of the bladder must be suspected and intraperitoneal as well as extraperitoneal rupture considered. 1 figure.

(Rupture of the bladder is a common complication of fracture of the pelvis, and the one which should always be looked for. As the author states, it is more common and more serious if the bladder is distended at the time of the fracture, because it is then lifted into the abdominal cavity, with extravasation of urine into the latter. The moral is that when our women folks start off on long motor trips it is a good plan to empty the bladder beforehand and not to allow it to become too full during the trip. Such advice is probably not in the best interests of the soft-drink stands along the highways.—Ed.)

CARCINOMA OF THE URETHRA IN THE FEMALE

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Royal Victoria Hospital, Montreal, Que.

Canad. M. A. J., 58: 29–33, 1948

A brief summary of the literature on carcinoma of the female urethra is presented and 6 cases of primary carcinoma of the female urethra are reported. Menville and Counsellor brought the total number of recorded cases to 149 in 1935. Walther, in 1943, stated that more than 275 cases were on record. Carcinoma of the urethra in the female is infrequently encountered, but is not unusually rare. It is definitely more common than in the male.

During the period from 1917 to 1946, there have been 7,147 female admissions to the urological service of the authors' hospital. Of these, there were 9 cases of carcinoma in the female urethra, 6 of them being primary, or an incidence of 1 in 1,191.

The oldest of these 6 patients was 74 years, and the youngest 39. The average age was 63 years. The complaints in order of frequency were: increased urinary frequency, difficulty in voiding, complete retention, urethral discharge, painful micturition, hematuria, and urethral pain. Only one patient complained of a

palpable urethral mass. The average duration of symptoms was 2 to 4 months; however, one patient waited 2½ years before seeking help.

In all cases a more or less hard, fixed tumor was found at the urethral meatus. Some patients had extension to the adjacent vaginal wall and toward the bladder, but in no case was the bladder actually involved. Only 2 cases had inguinal adenopathy.

The results on the whole were poor. Two patients could not be traced. Three patients died 2 years 5 months, 2 years 3 months, and 6½ months, respectively, after the first examination. Only one patient is known to be alive after 5 years, and she is not free of the disease.

The diagnosis of urethral carcinoma in the female is usually made late, possibly because there are no characteristic symptoms. Early diagnosis can be made only by taking a biopsy of all growths about the urethral orifice, regardless of their benign appearance.

Treatment is usually palliative. The immediate problem of retention was usually treated by permanent suprapubic drainage. Excision and coagulation of the local growth produced the longest periods of freedom from evidence of disease. The inoperable cases were treated with radium or x-ray therapy in addition to electrocoagulation. In view of the marked change brought by x-ray therapy in a completely occluded urethra, the writers suggest that this agent should be given a real trial in the earlier cases in conjunction with excision and electrocoagulation.

Regular follow-up with periodic examination and coagulation of recurrences seems to have given the most encouraging results in this brief series. 3 figures.

(This is one of the types of cancer which is likely to depress the gynecologist, because of the difficulties of treatment. Fortunately, it is rare. Many of the cases are seen late, and adequate surgical excision is likely to be impracticable, especially as it would mean loss of urinary control and the creation of a suprapubic or vaginal fistula. It is well to remember that a urethral caruncle may undergo malignant change, and if a caruncle shows any unusual induration or infiltration, biopsy should be done before it is subjected to some such simple procedure as fulguration or excision. In a recent case of my own, there was no lesion of the meatus, but the carcinoma produced an enormous infiltration of the proximal 2/3 of the canal, extending upwards into the neck of the bladder. Radiotherapy gave temporary palliation but the patient died.—Ed.)

OPERATIVE GYNECOLOGY

THE ABUSE OF PELVIC SURGERY IN THE FEMALE

N. F. MILLER

University of Michigan Hospital, Ann Arbor, Mich.

The writer states that we may inquire whether medical knowledge has advanced sufficiently to render some of our time-honored operations on the female pelvic organs less desirable or even unnecessary, and asks whether increased knowledge regarding physiology of the generative organs calls for curtailment of surgical procedures.

Carpenter, in 1936, analyzed 1,137 separate gynecologic specimens from 11 general hospitals. He found the tissue distribution to be as follows: ovary, 28.3 per cent; tube, 20.3 per cent; uterus, 19.1 per cent; cervix, 16.9 per cent; and endometrium, 15.2 per cent. Changes noted in the 314 excised ovaries were as follows: follicle cyst, 57.0 per cent; simple cyst, 11.1 per cent; corpus luteum cyst, 10.8 per cent; chronic oophoritis, 10.3 per cent; hemorrhagic cyst, 5.1 per cent; pseudomucinous cystadenoma, 1.0 per cent; carcinoma, 0.6 per cent; Krukenberg tumor, 0.6 per cent; fibroma, 0.6 per cent; dermoid tumor, 0.6 per cent; and granulosa tumor, 0.3 per cent.

Mengert reported that of 1,320 ovaries examined at one hospital, nearly 75 per cent were normal or contained follicular or corpus luteum cysts.

On the basis of the author's experience and that reported by others, there would seem to be little reason for oophorectomy because of minor palpable cystic change. This attitude, of course, does not apply to ovaries showing progressive enlargement beyond 5 to 7.5 cm. nor in solid ovarian tumors. No surgeon is properly equipped to perform oophorectomy until he is familiar with knowledge concerning normal physiologic variations in size and the ovary's important hormonal function in maintaining normal health.

Similarly, the uterus also suffers from unnecessary extirpation. Regardless of whether or not future study proves any physiologic importance of the uterus after the child-bearing years, excision of this organ in the absence of disease is no more justified than removal of the normal breast.

In a previous study by Miller (Am. J. Obst. & Gynec., **51**: 804, 1946; abstracted in Survey, **1**: 760, 1946), 246 hysterectomies performed during 4 months in 10 Midwestern hospitals were analyzed. In 49.6 per cent of patients the clinical diagnosis was confirmed. In 17.4 per cent, the clinical diagnosis was not corroborated, but the operation was considered justifiable. In 32.8 per cent there was either no disease or else disease contraindicating hysterectomy.

In conclusion, the author notes that some hospitals have taken steps toward improvement by forming tissue study committees, while in others, preoperative

consultation is required. Although these measures will serve to reduce nonindicated surgery, they appear to be poor substitutes for universal acceptance of sound surgery based on careful preoperative study and diagnosis.

(The author of this paper, himself an exemplar of the conservative school of gynecology, has been carrying on a little crusade against the abuse of surgery in gynecological practice, and has brought much evidence to substantiate his view that such abuses exist. I believe that every sensible person would concede this point even without statistics. Everyone knows that innumerable uteri and ovaries are removed, just as are any number of appendices and tonsils; but, suggestive as are the figures based on the pathological examination of removed tissues, they cannot be expected to give an accurate idea as to the extent of unnecessary surgery.

For example, all of us will remove perfectly normal tubes and ovaries when a carcinomatous uterus is removed, and most of us see no advantage in leaving the ovaries in the case of women over about 45 if hysterectomy is necessary for large myomas. No one has ever demonstrated any functional value in the postmenopausal ovary, while on the other hand such ovaries are not infrequently the seat of cystadenoma and carcinoma. In somewhat younger women, some will deliberately remove one of the normal ovaries, with the view that one ovary is all that is necessary for internal secretory purposes, and the removal of the other will divide by two the chances of later ovarian neoplasm. Such removed organs are properly reported as normal by the pathologist, but in such cases the surgeon need feel no culpability. The same general statement may be made concerning at least a small proportion of removed uteri.

This, however, does not lessen the justifiability of the author's general criticism. Myomas may very often be treated expectantly, and in younger women myomectomy is often the proper procedure when operation is indicated, rather than the hysterectomy which seems to be almost routine with some surgeons. Again, there is no doubt that there is too much tinkering surgery in the form of resections and removal of ovaries because of the so-called cystic degeneration which is usually an entirely normal process. These examples might be extended at great length. I suspect that the general surgeons who throughout the country do a large fraction of our gynecological surgery are major offenders along these lines, though, the Lord knows, our own skirts are far from clean.—Ed.)

CULDOSCOPY, A USEFUL GYNECOLOGIC PROCEDURE

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During the past year the writers have made frequent use of the culdoscope, and have come to regard it as a valuable diagnostic aid in gynecologic patients. The present paper is a report of their experience in 56 cases.

The patient is placed in the knee-chest position and the vagina cleaned as for a vaginal plastic operation. Many patients have been examined under local anesthesia, several cc. of 0.5 per cent nupercaine solution being injected in the posterior fornix. For general anesthesia, intravenous pentothal sodium is used. All patients are hospitalized for at least 24 hours. With the patient in the knee-

chest position, the perineum is retracted to permit air to enter the vagina. The spot at which puncture is made is shown in the authors' illustration. When the obturator is withdrawn from the trochar, there will be an audible in-rush of air if the tip of the cannula is in the cul-de-sac. The sterile culdoscope is then introduced through the cannula. The uterus, tubes, ovaries, broad ligaments, uterosacral ligaments, infundibulopelvic ligaments, rectal wall, sigmoid, small intestines, and often the cecum, appendix and ureters can be visualized. If the object is to inspect the tubes to determine points of obstruction, a weak solution of methylene blue is introduced through a self-retaining cervical cannula; distention of the tube can be seen proximal to the point of obstruction. At completion of the examination, the culdoscope is withdrawn, but the cannula is left in place while the patient assumes the lateral recumbent position. Pressure on the abdomen exhausts the air from the abdominal cavity. The wound in the cul-de-sac is not sutured.

The greatest indication the authors have found for culdoscopy (and the indication in 37 of the 56 cases herein reported) is to gain more information in cases suspected of having tubal pregnancy. Of the 37 patients culdoscoped because the history and/or pelvic findings suggested tubal gestation, a diagnosis of tubal pregnancy was made in 5 instances. In each case operation confirmed the diagnosis. None of the 32 cases in which tubal pregnancy was excluded was found to have it by subsequent operation or observation.

Salpingitis was found to be the condition simulating tubal pregnancy in 18 of the 37 cases. There were 3 cases of retained placental tissue, one early intrauterine pregnancy, 3 follicular retention cysts, one large corpus luteum, one case of endometriosis and 5 cases diagnosed as unexplained abdominal pain. Culdoscope observations were substantiated by subsequent operation or observation.

Culdoscopy is also of value in deciding whether a given patient warrants laparotomy for atypical lower abdominal pain, or whether she should be placed in the psychosomatic class. In severe cases of dysmenorrhea, culdoscopy reveals very early endometriosis when it exists. Differentiation between salpingitis and endometriosis is easily made by culdoscopic examination. Information may also be obtained for differentiation between early acute salpingitis and acute appendicitis. Differentiation between a retention cyst or cystic ovary and a neoplasm is easily made through the culdoscope. The possible existence of an early nonpalpable adnexal neoplasm in cases of postmenopausal bleeding can be determined by culdoscopy. In certain endocrine disturbances, knowledge of the anatomic and physiologic conditions of the ovaries can be learned by culdoscopy. Finally, the culdoscope is of value in investigating sterility.

Contraindications to culdoscopy are: the presence of a fixed mass in the cul-de-sac, vaginitis, and occasionally a much contracted senile vagina. Culdoscopy was totally unsatisfactory in 2 of the 56 cases because of a fixed mass in the cul-de-sac. In one other case, cul-de-sac adhesions made examination entirely unsatisfactory. In a few other cases it was only partially satisfactory because of adnexal adhesions. There was no instance of hemorrhage, peritonitis or injury to a viscus. 14 figures.

(It is too early as yet to evaluate the diagnostic value of this procedure. The authors present their results with commendable conservatism. It would seem that in a limited group of cases the procedure might prove to be of genuine auxiliary and at times decisive value. Since the original publication of Decker, describing the instrument and the technique for its employment, the procedure is being tried out in a number of clinics, and within a few years we shall be better able to judge whether it is to be a valuable part of the gynecologist's armamentarium. Thus far, and this is certainly no reflection on those who have used the instrument, it is quite certain that, like a new toy, it is being used in quite a number of cases as an added stunt to give practice in the technic rather than because of diagnostic necessity.—Ed.)

PELVIC SYMPATHECTOMY

G. G. LENNON

Oxford

Brit. M. J., 2: 1057, 1947

The writer refers to the article by J. P. Greenhill in a previous issue, in which pelvic sympathectomy is advised "in cases of endometriosis in which conservatism is advisable." Lennon agrees wholeheartedly, and has practiced this for some time; in addition, he suspends the uterus to prevent retroversion due to adhesions. However, he does not think that Greenhill's technique goes far enough, since he does not completely denervate the ovaries.

Mitchell summarizes the nerves to the ovary as follows: (a) a superior group from the intermesenteric nerves and from the renal plexus; (b) a middle or intermediate group from the superior hypogastric plexus or from the hypogastric nerve. Therefore, in addition to presacral neurectomy, Lennon feels it advisable to incise the infundibulo-pelvic ligaments to complete the pelvic sympathectomy.

(The additional step of incising the infundibulopelvic ligaments when presacral neurectomy is performed does not seem rational in the cases of primary dysmenorrhea for which sympathectomy is most often done, as there is no reason to believe that the ovaries are the seat of the pain. Whether it would improve the results in ovarian endometriosis, in which sympathectomy is often advisable as a supplement to the primarily indicated surgical procedure, I do not know.—Ed.)

OUR EXPERIENCE WITH THE SPALDING-RICHARDSON OPERATION IN THE TREATMENT OF GENITAL PROLAPSE

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The authors stress the difficulty in dealing with genital prolapse associated with myomas or adnexal diseases, although this combination is by no means frequent. They follow the Spalding-Richardson technic: the vesico-vaginal fascia is prepared and the cervix and the supraisthmic portion of the body of the uterus are amputated. The adnexa may or may not be excised, according to the case. The round ligaments are attached to the uterine stump, and the latter is inserted between the bladder and the vagina, as in the Schauta-Wertheim operation. The authors call attention to some modifications of the original technic, according to the conditions of the individual case. Thus, in 7 instances, they were able to obtain good results by suturing the uterine stump to the fixed portion of the vesical peritoneum according to Halban's technic, whereas Te Linde attaches it to the pubic arch. As a final step of the operation, the perineum is taken care of. This operation was employed by the authors in 10 cases, 2 of which were followed by complications. One case developed peritonitis and another revealed a pelviperitoneal exudative condition. Late results were favorable.

(It is probably too early to predict the final position of the Spalding-Richardson procedure in the treatment of prolapse, whether or not the latter is complicated by myoma. Thus far I believe it fair to say that the operation has not received wide acceptance, most gynecologists preferring some type of Manchester-Watkins procedure or vaginal hysterectomy for the prolapse, and vaginal hysterectomy for prolapse complicated by moderate sized myomas. Few practice the vaginal operation for large tumors necessitating morcellation, though this has been extensively practiced in some of the European clinics. Most of us would feel, however, that it is more of a surgical stunt than a wisely considered procedure. All in all, the presence of a moderate sized myoma in association with cystocele, rectocele and prolapse of some degree would seem to provide an ideal set-up for vaginal hysterectomy, and this would be my own preference, with of course correction of the cystocele and rectocele.

This is not to say that the Spalding-Richardson procedure does not give good results, because I am sure that it does. But it is a time-consuming operation, and not free from postoperative complications, such as hemorrhage. The proponents of vaginal hysterectomy can properly claim that this operation is much simpler, and that with proper care of the uterosacral ligaments and the obliteration of the cul-de-sac, the risk of postoperative enterocele is very greatly minimized, though not altogether eliminated. The follow-up studies of this plan, as reported in the literature, and this has been my own experience, have shown excellent results. Similar good results are seen with the Manchester operation, which, incidentally, can be easily combined with myomectomy in certain cases. It is possible that the Spalding-Richardson operation may achieve wider adoption in the future, but, as mentioned above, it is too early to make predictions at this point.—Ed.)

SYMPATHECTOMY AND INTRASPINAL ALCOHOL INJECTIONS FOR RELIEF OF PELVIC PAIN

J. P. GREENHILL

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The author briefly describes 2 procedures which may be used to relieve intractable pelvic pain in women. In the category of those who suffer severe pelvic pain, and in whom removal of its cause is impossible or inadvisable, are: women with inoperable carcinoma of the uterus or severe dysmenorrhea, women subjected to repeated unsuccessful laparotomies for pelvic pain, and young women with endometriosis who should not be castrated. The 2 methods of pain relief for these cases described by the writer are pelvic sympathectomy and intraspinal injection of alcohol.

Pelvic sympathectomy has proved most helpful in cases of uterine carcinoma, dysmenorrhea, endometriosis and pelvic pain of unknown etiology. In inoperable cases of cancer pelvic neurectomy is helpful not only for relief of pain but also as a prophylactic procedure at the time of hysterectomy. Pelvic sympathectomy will relieve the pain in about half the cases of Group III and Group IV cervical cancer, and will partially relieve many more. Sympathectomy is of great value in conservatively treated cases of endometriosis, not only for pain relief, but also because it apparently improves the endometriosis. Nearly all cases of severe primary dysmenorrhea can be cured by sympathectomy, but this operation should not be done until all conservative measures have proved futile. Finally, in cases subjected to numerous laparotomies without relief of pain, pelvic sympathectomy will yield spectacular results. The technique of pelvic sympathectomy described by the writer is that recommended by Cotte (1931, 1932).

Intraspinal (subarachnoid) injection of alcohol is a much simpler procedure than that of pelvic sympathectomy and does not even require hospitalization. Furthermore, the author has found that the percentage of patients with uterine carcinoma who obtain relief is higher than with pelvic sympathectomy. Injection is made in the second, third, or (usually) fourth lumbar interspace. Procaine is injected into the skin as for ordinary lumbar puncture. When the needle is in the subarachnoid space, as shown by the flow of spinal fluid, 0.75 ml. of absolute or 95 per cent alcohol is injected very slowly into the cerebrospinal fluid. For the injection, the patient should lie on the side opposite to that in which most of the pain is present, and the results are better if she remains on that side for some time after the injection. Because this procedure may injure the spinal cord, it should not be used for any individual except one with cancer.

(Pelvic sympathectomy is undoubtedly of frequent value in the treatment of pelvic pain conditions, but the author, in his statement that "nearly all" cases of severe primary dysmenorrhea can be thus cured, is more optimistic than most other authors, the usual cure rate being put at from 60 to 70 per cent. I do not see why the operation should actually improve endometriosis, and I have made no such observation myself. But it does usually relieve the pain which these patients might otherwise still have when conservative operations are done, as they should be in younger women. As I have previously stated in these columns, it has seemed to me that sympathectomy done in this supplemental fashion, in cases in which there is some other primary indication for laparotomy, but in which there is some doubt that without sympathectomy the primary procedure will relieve the dysmenorrhea, has a wider applicability than sympathectomy per se. This has certainly been the case in my own practice.

It is hardly necessary to emphasize again that sympathectomy should not be resorted to in dysmenorrhea unless simpler methods do not suffice to relieve or greatly mitigate the menstrual pain, as they most frequently do. There is no question, however, of its frequent efficacy when indicated and when properly done.

As for sympathectomy in advanced cancer, I do not feel so enthusiastic, not only because the results are not by any means certain, but because one dislikes to recommend an abdominal procedure in these hopeless patients just on the chance of temporary relief from pain. If the use of analgesics, with all its disadvantages, does not sufficiently lessen the patient's pain, intraspinal injection of alcohol would seem definitely preferable to sympathectomy.—Ed.)

RELIEF OF PAIN IN INTRACTABLE CANCER OF THE PELVIS

M. KENNY

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Brit. M. J., 2: 862–863, 1947

The author considers that the treatment of patients with intractable cancer of the pelvic organs, in respect to relieving them of pain before death, is surely a part of the treatment of cancer, yet little is written of the means of relief in hopeless cases. In this paper is described a means of relief which has been given careful trial and which is recommended for effect and simplicity and because it can be repeated as necessary until death. This is the method of caudal analgesia.

The technic of caudal analgesia is described in some detail. Following preparation and correct positioning of the needle, proctocaine is injected to an amount varying with the skeletal size of the patient, usually 40 to 60 ml. When the patient expresses relief of pain, or if the level of skin anesthesia rises to nipple level, the injection is stopped.

The writer and his assistants have so treated 17 patients with cancer of the uterus, bladder, prostate and vagina. Of these, one man with prostatic cancer, who had been incapacitated for 3 months, was able to return to his work as a milk-roundsman for the rest of his life (nearly 7 months) after only one injection of 50 ml. of proctocaine. A 46-year-old woman with cervical cancer died quietly of

cardiac secondaries after 2 injections of 40 ml. of proctocaine, 9 weeks after her first visit.   The duration of relief with one to 3 injections varied in 11 others from 3 weeks to 4 months; in all but 4 this marked their natural term.   The 4 developed painful secondaries in other regions.

Two women with pelvic secondaries from uterine cancer had apparent relief for a few days, but on return of symptoms failed to be relieved by further injection.   One man with prostatic cancer with spinal metastases was not relieved at all.   The only fatality was a man with extensive invasion of the abdominal wall by bladder cancer, who died apparently from exhaustion and hemorrhage under thiopentone anesthesia, given before the caudal injection, as in no other way could the patient bear to turn on his side.

No instance of urinary or fecal incontinence was seen following caudal injection of proctocaine, with or without alcohol.

(Everyone nowadays is interested in the diagnosis and treatment of pelvic cancer in its early stages, and, in the case of uterine cancer, of its very earliest, even preinvasive stage. This is all to the good, and such concentration of diagnostic effort, if supplemented by such widespread popular education as is now being carried on, justifies the hope that the coming years will show a higher incidence of very early, favorable cases than has thus far been achieved.

But the country is full of cancer wreckage, in the form of thousands of patients awaiting death from hopeless cancer.   This has always been the case and this will undoubtedly be the case for many years to come.   In thousands of homes these tragedies are being acted out to their inevitable and bitter end, with an untold aggregate of physical agony to the patients and just as much mental distress on the part of the loved ones who have to stand by so helplessly.

It is this late, hopeless, painful stage which, it seems to me, has received only left-handed attention from our profession.   Everything possible in the way of radiotherapy and surgery is apt to be done before this is reached, but all too often, in nearly ¾ of cervical cancer cases, the patient is likely to be abandoned by the gynecologist, and turned back to the family and the family doctor to end her days.

The customary plan is to keep the patient as nearly comfortable as possible, and morphine and other narcotics sooner or later are resorted to.   As a matter of fact, the attitude of most families is that since the patient cannot get well, the next best thing is to keep her as nearly free from pain as possible, even though this plan may at times shorten her life somewhat.   A crying need in this country is a larger number of hospitals willing to accept these hopeless cases, mitigating the problem for both the patient and her family.   In my own community, for example, only a handful of beds are available for this purpose, and this must be the case in many other communities as well.

The method of caudal anesthesia, as described by the author, appears to have been very helpful in the cases he reports, although it is difficult to understand why the relief of pain is of such long duration.   Chordotomy, advocated by Grant a good many years ago, is probably more effective, but it is a formidable procedure which seems to have met with no general acceptance.   Sympathectomy likewise is an abdominal procedure, though much simpler than chordotomy, and therefore more often used.   Intraspinal injection of alcohol is the method which has been perhaps most frequently resorted to, and perhaps caudal anesthesia, as recommended by Kenny, may prove to be a good alleviative.   But I suppose the majority of these hapless patients will still be tided over to the inevitable end by the narcotic route.–Ed.)

GYNOGRAPHICS

E. M. GREENBERG

New York, N. Y.

Am. J. Obst. & Gynec., 54: 1081–1082, 1947

The author suggests that history-taking in obstetrics and gynecology might gain by the use of a system of gynographics, which he defines as "symbolism in obstetrics and gynecology." Such a system is not entirely new to these specialties; for instance, the Roman symbols for Mars and Venus have long been used for denoting the male ($\circlearrowleft$) and the female ($\circ$).

The important gynecologic and obstetric symptoms and signs can be broken down into a relatively small number, and translated into symbol form. The writer presents a key to such symbols. The advantages of gynographics are speed of recording, speed of interpretation, conciseness, clarity and comprehensiveness, signs and symptoms in sequence at a glance, and universality of language. 1 figure.

(The author must have had a lot of fun devising the symbols for various gynecological symptoms, and the reader likewise can get some amusement from looking them over. Being one of those queer individuals who do not like to see in any sort of medical writing too many abbreviations, such as D & C., S.O., m.p., etc., I can imagine how unhappy I would be to read a paper or even a simple office history loaded with the wondrous symbols proposed by the author. That for coitus is evidently a spermatozoon or a viper, all coiled up and ready to strike. That for dyspareunia resembles a spermatozoon with a broken back, possibly meant to represent the trauma sustained in trying to overcome serious opposition. Many of the symbols look for all the world like Egyptian hieroglyphics, and I can imagine what a problem is going to be posed for some archeologist of A.D. 5000 if he happens to dig up the buried records of Dr. Greenberg's office. Perhaps some medical secretaries will have to add this new system of shorthand to their many accomplishments, but I have given my own a solemn promise that she need have no fears on this point.—Ed.)

BOOK REVIEW

A TEXTBOOK OF GYNECOLOGY

JAMES YOUNG, D.S.O., M.D., F.R.C.S.E., F.R.C.O.G.

Professor of Obstetrics and Gynecology, University of London; Consulting Gynecologist, Royal Infirmary, Edinburg, etc.

Seventh Edition

Published by Adam & Charles Black, London

The first edition of this work appeared in 1921 and the fact that it has now gone through seven editions is ample proof that it has been well received. It impresses the reviewer as the best of the British textbooks on gynecology which he has seen, and the one which would most clearly meet the requirements of the student and general practitioner, for whom it is primarily intended. It is the sort of book, however, which the specialist also will wish to have on his bookshelf.

The author's style is simple and attractive, his discussions of the various subjects clear and systematic, and the 277 illustrations helpful in the clarification of the text. For the most part they are at least fairly good, although some of the photomicrographs are too small to be of much value.

The book is divided into 9 chief sections. The first 2 present brief but adequate summaries of Anatomy and Physiology and Examination of the Patient, respectively. Succeeding sections deal with Disorders of Function and Symptoms Found in Gynecological Disease, Displacements of the Uterus and Allied Conditions, Infections, Extrauterine Pregnancy, New Growths, Development and Errors of Development, and Operative Gynecology.

Especially satisfactory is the author's handling of the rather difficult and complex subject of functional disorders, embracing the troublesome subject of endocrine therapy, which is presented sanely and conservatively. One can of course pick out minor points for criticism, such as the recommendation of plugging of the vagina for puberty bleeding. Incidentally, like most British authors, Young prefers the term "metropathia hemorrhagica" for the most common type of functional bleeding, and makes no mention of the fundamental characteristic of this group, the fact that it represents an aberration of the anovulatory type of cycle.

A less forgivable defect is the entire omission of any discussion of the earliest phases of cervical carcinoma, without even any mention of the precursory and pre-invasion stages which are now so extensively discussed in the literature. For the most part, however, the subjects are brought reasonably up to date, though it may be an indication of British conservatism to hang on to certain measures of treatment now pretty generally discarded in this country.

The section on Operative Gynecology appears to be presented rather apolo-

getically, the author stating that he "believes that much of the time which undergraduates spend in the operating theatre is wasted." With this view the reviewer is in full accord, and he believes that Young's book would be improved by entire omission of operative details. This chapter, as might be expected from the author's expressed sentiment, is written in a rather perfunctory manner, with very inadequate illustrations.

Finally, it seems to the reviewer that the value of the book would be definitely increased if at least a brief list of the more worthwhile references were appended to the various chapters. On the credit side, the book is full of meat, and an amazing amount of information is packed within its 459 pages. It may be recommended as a worthwhile addition to the library of students, general practitioners and specialists.

EDMUND R. NOVAK

AUTHOR INDEX
JUNE, 1948

Obstetrics

THE PERMEABILITY OF THE HUMAN PLACENTA TO SODIUM IN NORMAL AND ABNORMAL PREGNANCIES AND THE SUPPLY OF SODIUM TO THE HUMAN FETUS AS DETERMINED WITH RADIOACTIVE SODIUM

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AND G. J. Vosburgh

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University and Hospital.*

Changes in rate of placental transfer per unit weight of placenta were measured in normal pregnancies, and a small number of abnormal pregnancies, using radioactive sodium, from the 9th week of gestation until term. The following problems were set forth: measurement of the permeability of the normal human placenta to sodium from early in gestation to term; comparison of the permeability of the human placenta with that of other placentas of the hemochorial group; measurement of the effects of disease on placental permeability; and evaluation of the supply of sodium to the fetus as this is related to the requirement for sodium during fetal growth.

The human placenta, like all placental types which have been studied, shows a great increase in permeability to sodium—as it appeared in this study, permeability increased about 70 times from the 9th to the 36th week of gestation. From the 36th week to term there was in all but 1 case a rapid decrease in permeability, most marked in a single case of twins. These changes can be correlated with morphological changes which occur in the placenta during the process of aging. The terminal sharp decrease in permeability is undoubtedly largely due to deposition of fibrinoid over the surface of the villus.

The 4 placental types classified by Grosser can be readily distinguished by the differences in their permeabilities. It is evident in this study that the permeability of the placenta of man to sodium agrees closely with other members of the hemochorial group.

The permeability of the placentas from 5 patients with hypertension and 2 with cardiac disease was found to be normal. A reduction of transfer rate was noted in 1 of 2 cases of pre-eclampsia, and the rate was low in the single case of twins which was studied. More experience with tracer materials is needed for conclusions.

In the 2 cases where transfer was observed during normal labor during the half-hour or hour preceding delivery, there was no decrease in transfer rate. Also, there was no evident difference between the transfer rates when spinal or caudal anesthesia was used and when general anesthesia was obtained with sodium pentothal or gas-oxygen-ether.

In respect to fetal nutrition, the lowest safety factor (ratio of the amount of a substance retained by the unit weight of fetus in its growth) observed for sodium has been 3.5 in the sow. The highest safety factor reported prior to this study was an average of 50 in the guinea pig. According to this report, man has a safety factor varying from 160 at 12 weeks to over 1100 at term—less than 0.1 per cent of the sodium reaching the human fetus at term is retained. Man is unique also in that sodium is supplied at a constant rate, about 0.9 mg. per gm. fetus per hour, from the 12th week when the fetus is reproducing its weight at the rate of about 12 per cent per day to term when the daily weight increase is only about 1 per cent. This is the single exception so far found to the hypothesis that the fundamental principle underlying placental function is that the rate at which substances are transferred to a unit weight of fetus shall parallel the relative growth rate of the fetus. 3 figures, 2 tables.

(A 70-fold increase during pregnancy in the rate at which a gram of placenta transfers sodium, may seem on first consideration an unwarranted extravagance. Actually, a little calculation will show that it is precisely what is required if the supply of this element per gram of fetus is to be kept constant. This circumstance is attributable, of course, to the fact that the fetus increases in size very rapidly in comparison to placental growth. Let us take, for example, a period over which dependable weights for fetus and placenta are readily available. A fairly standard figure for the weight of the fetus at the 12th week is 20 Gm. and of the placenta, 36 Gm. (Needham, Joseph: Chemical Embryology, Cambridge, 1931, p. 1677). The weights reported in the above paper for cases at this stage are in good accord with these figures, namely, 19 and 14 Gm. for the fetuses, and 34 and 34 Gm. for the placentas. Since the average fetus at term weighs about 3300 Gm., this increase from 20 Gm. over the 28 weeks would be 165 fold, whereas the augmentation in placental weight from 36 to 500 Gm. at term, would be only 14 fold. Therefore, between the 12th week and term, the fetus grows 12 times more than the placenta. Turning now to the authors' figures for this specified period, we find that the sodium supplied per gram of placenta per hour rises from 0.44 mg. to 5.3 mg.,—or exactly 12 fold. In other words, this great increase in placental permeability to sodium as pregnancy advances, is simply a compensatory mechanism (but how wondrously precise a one!) for offsetting the diminishing relative size of the placenta.

The original paper includes photomicrographs showing the mechanism by which this increase in permeability is brought about. The chief factors concerned are: (1) a great increase in the surface area of the chorionic villi as gestation advances due to a progressive increase in the number of villi and a decrease in their individual size; (2) a thinning of the villous walls including disappearances of the Langhans layer; and (3) an increase in the number of fetal capillaries within the stroma of the villus together with a decrease in the thickness of the capillary walls.

Curious is the authors' observation that the human fetus is apparently unique in receiving a constant supply of sodium according to its weight at any given time. In the other species studied by the authors, the supply parallels the relative rate of growth. Since the other species studied include the rat and guinea pig (that is, rodents which, like man, have a hemochorial placenta) it would appear that the hemochorial placenta does not behave identically in all species,—another problem for future investigation.

In previous editorial notes I have commented on the rich possibilities which lie in isotope research on placental interchange, physiology of the fetus and other phenomena of pregnancy. This paper is a good example not only because it illustrates the precision of the method but, more important, because it uncovers a new body of knowledge concerning which we have hitherto only ventured to guess.—Ed.)

HORMONE SECRETION BY HUMAN PLACENTA GROWN IN TISSUE CULTURE

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Recent endocrinological studies have brought forth some direct evidence of the secretory function of the placenta. This report is presented as further direct indication of the secretion of the gonadotrophins and estrogens by human placental tissue grown in tissue culture.

Placental tissue was collected under sterile conditions in the operating room from patients requiring therapeutic termination of pregnancy. Normal appearing fragments were selected and transferred immediately to the tissue culture laboratory. The tissue culture method used was that originated by Löwenstädt, as suggested to him by Carrel and later revised by Gey with subsequent modifications by Lewis.

Histological sections of both the early and the more mature placental tissue revealed normal tissue free from any abnormality. The control tissue washings (on mouse spleen or lung tissue), made at intervals during the study, showed complete absence of any chorionic gonadotrophin and estrogen activity when injected into test animals.

The placental tissue studies revealed that in the early stages of growth 3 types of cells could be readily identified: stromal cells with a round nucleus, syncytial cells which are oblong and have an oval nucleus, and Langhans cells which are more or less round and have a round nucleus surrounded by a pale halo. After a few days the latter cells predominated. Soon a direct relationship was noted between any increase or decrease in the hormone titrations for the gonadotrophins and the Langhans cell growth, suggesting that these cells are probably responsible for the great amounts of this hormone produced during pregnancy. It is reasonable to assume that the relatively lower level of the blood and urinary levels of gonadotrophins in later pregnancy fall in direct correlation with the fewer number of Langhans cells. These results support those of Gey and his coworkers.

The preoperative serum assays done for the estrogenic hormone were small in amounts until the 3rd month of pregnancy. Syncytial cells, believed to be the source of estrogen formation in the placenta, were noted in the early stages but were quickly excluded by the Langhans cells. In the placenta tissue culture

assays many estrogen determinations were made without evidence of its presence; however, these negative results are felt to be inconclusive, since so little increase in estrogen was present in the blood of the patient prior to termination of pregnancy and since the syncytial cells did not grow in tissue culture.

Curves of estrogen in the blood and urine of normal pregnant women show a gradual rise from the 3rd month to the highest peak just prior to parturition Therefore, attempts were made to grow the more mature placenta of 8 or 9 months. The growth was unsuccessful because, in marked contrast to rapid growth of the trophoblastic tissue of early pregnancy, fibroblasts grew in profusion without demonstrable syncytial or Langhans cell growth. 4 tables, 8 figures.

(The findings in this study, namely that the Langhans cells are responsible for the manufacture of chorionic gonadotrophin, constitute a convincing confirmation of the histochemical observations of Wislocki and his associates who likewise found this layer to be the site of production of this hormone. The fact that these two quite different techniques yield the same result on this point seems to leave this question rather conclusively settled.—Ed.)

RECORDING UTERINE CONTRACTION PATTERNS IN PREGNANT WOMEN: APPLICATION OF THE STRAIN GAGE IN A MULTICHANNEL TOKODYNAMOMETER

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Present methods of studying and recording uterine activity in women during the latter part of pregnancy are essentially of 2 types. One records pressure from a single isolated region transmitted to a tokograph which is applied to the abdomen externally. The other measures changing pressures by means of a balloon placed within the uterus during the course of labor.

A new method of recording uterine activity has been designed and yields information continuously concerning the nature of the activity in several parts of the uterus. This instrument which has been designated a *tokodynamometer,* records electrically on a single piece of moving paper the uterine activity at each of 3 selected points of the abdomen. The principle employed involves application of the strain-gage dynamometer to direct electrometric recording through frictionless writing.

The pick-up device is a Statham strain-gage dynamometer. This is mounted on a heavy brass ring so that the sensitive element of the gage is connected by a simple lever system to an adjustable plunger held vertically in the center of the

ring. Each of the 3 rings is held in place on the abdomen by double-coated Scotch tape applied to the under side.

The input current of each strain-gage is derived from a 6-volt A battery. The output from each gage goes directly to a Weston microammeter modified in such a way that it is balanced with a fine quartz tubing extension on its indicating arm. On the end of each of these is a small piece of 36-gage nichrome wire mounted vertically like a cross on a T.

The recorder operates by distributing sparks through each of the 3 nichrome wire tips at half second intervals. The sparks pass from a plate above to a plate below while a specially treated heat-sensitive paper passes over the lower plate at any desired rate. The tips of the ammeters swing freely between the metal plates and over the paper without touching either, i.e., by frictionless writing. The instrument is so sensitive that the top of the unit is enclosed in a plastic case during the recording to prevent disturbance from air currents. The records of uterine contractility consist of a series of fine holes burned through the paper in the position under the nichrome tip according to its position at the instant of sparking. Before use, the sensitivity of each gage is set by varying the current input so that a 50-gram weight hanging on each gage lever causes deflections of the same size in each channel.

In operation, the gages are attached to the abdomen and adjusted. By turning a single switch on the recorder the paper starts moving and the sparking mechanism begins to record. During the time of recording the patient may talk, cough or change her position without interference to the records of the uterine contractions. Rectal or vaginal examinations may be made and the rhythm of coordinated uterine activity continues without real interruption and may be observed by palpation to coincide with the record obtained on the TKD.

(We have been using the Reynolds' Tokodynamometer on our delivery floor since September, 1947 and feel that we have learned a great deal from it in regard to the dynamics of normal uterine contractions; and we hope that in time it may prove informative about the nature and prognosis of uterine inertia. The instrument records simultaneously contractions in the upper, middle and lower uterine segments and provides a graphic record of the fact that, for the best type of labor, a very nice correlation must exist between uterine behavior in these three areas. In most cases of false labor all 3 segments appear to contract simultaneously and to about the same degree. In true labor, the lower uterine segment shows no evidence of contractility while the upper 2 segments behave in a fairly characteristic fashion as follows: Contractions seem to be initiated in both simultaneously and to about the same extent, but the contraction in the midportion is brief, whereas that in the upper segment, continues for a decidedly longer period. Hence, during the latter half of a contraction only the upper portion of the uterus is in a state of contraction. This is of course the mechanism which one might theoretically visualize as promoting the most effectual stretching of the lower uterine segment, dilatation of the cervix and fetal descent. The factors concerned in uterine inertia, as recorded by this instrument, seem to vary considerably from case to case and it would appear that it is not a very homogeneous entity. However, the cases of this complication so far studied are few in number and more observations will be necessary before any definite statement can be made.—Ed.)

MANAGEMENT OF NORMAL PREGNANCY, LABOR AND PUERPERIUM

DIAGNOSTIC TEST FOR PREGNANCY UTILIZING THE MALE FROG AS THE REACTIVE ANIMAL

C. Galli Mainini

The author describes a new test for the diagnosis of pregnancy, in which the male frog is utilized as the reactive animal. This reaction is based upon the fact that the injection of pregnant urine promotes migration of spermatozoa from the testicle to the bladder of the frog, which are microscopically revealed in a few drops of urine obtained through catheterism. Based upon 99 tests performed, the author arrives at the following conclusions: (1) the injection of 10 cc. of a pregnant woman's urine into the lateral lymphatic sinus of the male frog leads to the appearance of spermatozoa in the urine of the latter; (2) in 99 tests performed simultaneously in the frog and in the rabbit, there were 94 coincidental results; (3) the appearance of spermatozoa in the frog's urine was observed within the following 3 hrs. of injection, in 47 positive cases. In any instance the cases which resulted negative within this period of time became positive within the 22 hrs. following the injection; (4) the duration of the spermatozoa in the frog's urine was determined in 18 tests, and the maximum time in which they were encountered was estimated in 50 hrs.; (5) as a matter of control, urine of normal children, men and women, of women beyond the menopause, men beyond 60 years of age and of patients with endocrinopathies was injected, and the results were negative in all instances; (6) injection of a unique dose of certain amounts of progesterone, synthetic and natural estrogens, testosterone, thyroxin, desoxycorticosterone, adrenalin and pitressin did not promote the appearance of spermatozoa in the frog's urine within 24 hrs.; (7) injection of chorionic gonadotrophin yielded positive results, whereas the pregnant mare serum gonadotrophin produced the reaction in only a few frogs; (8) temperature seems to constitute an important factor in the velocity of the reaction, the latter being slower at lower temperatures; (9) from the results achieved, it seems that this specific reaction may constitute the basis for a new diagnostic test for pregnancy, which has the following advantages: (a) velocity of reaction; (b) simple technic; (c) specificity; (d) exact appreciation of the element indicating the result of the reaction; (e) economy.

(The use of the male frog, *Rana pipiens*, as a test animal for the diagnosis of early pregnancy, as advocated by Mainini, is attracting widespread interest and two studies of the procedure in this country have confirmed completely the author's claims. One is the investigation made by Wiltberger and Miller of the Department of Zoology and Entomology

of Ohio State University and published in Science: *107*, 198, 1948. These authors reported tests performed on 200 animals and, provided the urines came from patients in the first trimester of pregnancy, no false negatives were obtained. Nor apparently were any false positives given by urines from non-pregnant persons. The authors point out, however, that the dependability of the test is limited to the first trimester since, later on in pregnancy, the low chorionic gonadotrophin content of the urine is not sufficient to give positive tests in more than 50 per cent of the cases.

The technique of the test as described by Wiltberger and Miller is simple and is as follows: A first morning (overnight) specimen of urine is obtained and 5 cc carefully injected subcutaneously into the dorsal or lateral lymph sacs of the frog. Two or more frogs are used since there may be a difference in the sensitivity to the test. Each frog is placed in a separate, clean, dry glass jar with a perforated lid and set aside for 2 to 4 hours at room temperature. At the end of this time any urine that has been voided by the frogs is examined microscopically. If spermatozoa are not present, the urine is carefully drained from the jar without disturbing the frog. The frog is then seized in the hand while still in the jar. This pressure usually induces another urination. The new specimen of urine is then examined for spermatozoa. The frog's sperms are easily identifiable. When spermatozoa are present, the test is positive; when they are not present the test is negative. The fact that there are no intergrades eliminates all subjective interpretations. The test animals are not killed and may be used for another test after 4 or 5 days.

The other paper reporting on the test is that by Robbins and Parker of the Mallory Institute of Pathology, Boston City Hospital (Endocrinology: *42*, 237, 1948). After simple filtration of the urine through ordinary filter paper, 5 cc of urine is injected subcutaneously into the dorsal lymph sac. No adjustment of the pH or control of temperature has been found necessary and the animals take this volume of fluid with great ease. Cloacal smears of the animal are then performed, beginning one hour later. This consists of aspirating the fluid in the external cloacal orifice with a glass capillary pipette. The fluid thus obtained is examined in a hanging drop preparation under reduced light. The spermatozoa are very easily seen, since they are large and the reactions are either all or none, producing either large numbers of sperm or none.

Robbins and Parker report results on 122 urines. Ten of these were obtained from normal girls having normal menses. The remaining 112 urines comprised 78 known pregnancy urines and 34 urines obtained from women with amenorrhe determined not to be pregnant by the Ascheim-Zondek test or its Friedman modification. No false positive reactions were encountered, but one false negative was observed on a urine from a patient who was only 2 weeks beyond her first missed period.

Although more experience with this test will be needed before final evaluation can be placed upon it, the several advantages it possesses make it very appealing. Not the least of these is the fact that these animals are easily obtainable in the United States and are very cheap. Moreover, positive reactions make themselves known within 2 to 4 hours, if we may judge by the American reports. Further investigation of this point, however, would seem to be in order since there is apparently a little discrepancy about the time factor between the statement of Mainini and that of the American observers. The fact that the test is not dependable in the latter part of pregnancy would not seem a very important objection from a practical viewpoint, but it is a circumstance which must be kept in mind if widespread clinical use of the test should come to pass. All in all, this appears to be a very promising diagnostic procedure and further reports will be awaited with much interest.—Ed.)

PATHOLOGY OF PREGNANCY

THE DETERMINATION OF THE PROGNOSIS OF PREGNANCY IN RHEUMATIC HEART DISEASE

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From October, 1939, to July, 1945, 131 women were observed through pregnancy and puerperium. In 11 other cases pregnancy was interrupted because the prognosis was considered unfavorable. In each of these cases sterilization was urged, for it was felt that one who was already a poor risk would be unlikely to improve as her heart disease advanced.

The 131 patients were delivered of 133 babies. These included 4 mothers who gave birth to twins and 2 mothers who died undelivered. There were 83 spontaneous deliveries, 39 forceps, and 8 breech deliveries. Cesarean section was performed on 3 patients for strictly obstetrical reasons. The authors could see no indication to recommend this procedure on a cardiac basis. The presence of rheumatic heart disease, per se, is no longer acceptable as an indication for cesarean section. It may occasionally be resorted to as a means of terminating prolonged labor in order to reduce the danger of heart failure. Authors reporting their own results in groups of patients where cesarean sections were done frequently as compared with those where it was done infrequently agree that the fatality rate is higher in the former group. This may be attributed in part to the fact that the greater risks were more likely to undergo section. It is, therefore, important to note that among patients with heart disease of equal severity (Classes 3 and 4) the death rate is significantly higher in the group delivered abdominally (hysterotomy or cesarean section) than vaginally.

Maternal Mortality. Table 1 lists the maternal mortality rate from rheumatic heart disease reported in the literature from 1936 to 1946, inclusive. Reports prior to 1936 were not included since they have been collected and published by Jensen (The Heart in Pregnancy, St. Louis, 1938, The C. V. Mosby Co.). Those after 1936 show a striking reduction in mortality rates; from 9.38 per cent for the period between 1890 to 1922 to 3.24 per cent from 1936 to 1946. This advance is very likely a result of better understanding of heart disease and its treatment, more skillful and conservative obstetrical management, a closer cooperation between the obstetrician and the internist, and the advent of chemotherapy.

In the authors' group there were 2 maternal deaths. One of their patients, 20 years of age, died of a staphylococcic bacteremia during the 5th month of her first

pregnancy. There was no discoverable focus of infection. The other patient, 33 years of age, died of heart failure in the 9th month of her 7th pregnancy. This patient was first seen by the authors at the end of her 6th pregnancy. At this time she manifested symptoms of diminished cardiac reserve and sterilization was therefore advised. The patient did not consent to this procedure, left the hospital, and did not report for postpartum care. She reappeared during the 27th week of her next (7th) pregnancy and was then in congestive failure. Immediate hospitalization was urged in vain. The next day she was admitted in pulmonary

TABLE 1

*Reported deaths among pregnant women with rheumatic heart disease (1936 to 1946)**

AUTHORS	YEAR	NO. OF PATIENTS	NO. OF DEATHS	PER CENT DEATHS
Hay	1936	66	1	1.5
Henderson	1936	76	2	2.6
Hagedorn	1937	50	5	10.0
Harris	1937	100	8	8.0
Lamb	1937	102	7	6.9
McClure	1937	69	3	4.3
Naish	1937	427	11	2.6
Pardee	1937	50	1	2.0
Carr	1938	44	1	2.3
Turino and Antony	1938	102	6	5.9
Lange	1939	322	6	1.9
Clahr, Klein and Greenstein	1940	181	4	2.2
Jensen, Wegner, Keys and Smith	1940	108	8	7.4
Gorenberg and McGleary	1941	345	10	2.9
Hamilton and Thomson	1941	781	37	4.7
Bramwell and Longson	1942	312	22	7.1
Brown and Sage	1942	32	1	3.1
Gorenberg	1943	223	8	3.6
Jones	1943	74	4	5.4
Sampson	1943	60	0	0.0
Mendelson	1944	1089	8	0.7
Scott	1944	114	3	2.6
Bunim and Rubricius	1947	142	2	1.4
Total		4869	158	3.24

* References given in original article.

edema. After several days of intensive treatment her condition improved. She was advised to remain in the hospital until term but she refused to do so. Several weeks later, the physician who had attended her at home reported that she died undelivered.

Infant Mortality. The infants delivered on the obstetrical service of Bellevue Hospital during the period of the authors' study were classified for the purpose of this analysis into 3 groups: infants of mothers with normal hearts, infants of mothers with rheumatic heart disease without failure, and infants of mothers with rheumatic heart disease with failure (Table 2). The mortality rate for

infants of mothers with compensated heart disease was not significantly higher than for infants of normal mothers. The mortality rate for infants of mothers with congestive heart failure, however, was 30 per cent, whereas in the compensated group it was 9 per cent and in those with normal hearts, 7 per cent. The difference and the standard error between the compensated and decompensated groups just falls short of being statistically significant (21 ± 11.1).

TABLE 2

Effect of heart failure on infant mortality: percentage distribution

	INFANTS DELIVERED OF NORMAL MOTHERS OCT. 1939 TO OCT. 1943		INFANTS DELIVERED OF MOTHERS WITH HEART DISEASE BUT NOT IN FAILURE		INFANTS DELIVERED OF MOTHERS IN HEART FAILURE	
	No. of infants	Per cent	No. of infants	Per cent	No. of infants	Per cent
Total number of infants delivered..................	6263	100	115	100	18	100
Born at term alive and well...	5452	87	97	84	12	66
Premature births alive and well......................	392	6	8	7	1	6
Stillbirths, viable.............	129	2	3	3	2	12
Stillbirths, nonviable.........	174	3	5	4	1	6
Neonatal deaths.............	116	2	2	3	2	12

TABLE 3

Effect of advancing pregnancy on heart failure

WEEKS OF GESTATION	NUMBER OF PATIENTS IN FAILURE
1– 4	0
5– 8	0
9–12	0
13–16	0
17–20	3
21–24	1
25–28	3
29–32	2
33–36	3
37–40	5
Postpartum	1

The expected date of delivery was taken as the end of the fortieth week of gestation.

Congestive Heart Failure. Eighteen of the 131 patients developed congestive failure during pregnancy, an incidence of 14 per cent. The criteria for congestive failure were pulmonary edema, paroxysmal nocturnal dyspnea, basal rales, or a palpable, tender liver. Failure occurred most frequently during the second half of pregnancy (Table 3). It should be noted that more instances of failure occurred in the last lunar month than in any preceding month.

The interval of time from the onset of the first rheumatic manifestation to the observed pregnancy was determined in 103 patients. As the interval lengthened,

the incidence of failure increased. Of those who had had rheumatic fever for less than 10 years, 4 per cent went into failure; whereas, of those who had had it longer than 15 years, 18 per cent or more became decompensated. The authors' data show that about ¼ of the patients above the age of 30 years, or those who had had rheumatic fever for more than 20 years, developed congestive failure during pregnancy.

A close relationship was observed between the limits of cardiac reserve that existed before pregnancy and the incidence of failure during pregnancy. Only 1 of the 82 patients in Class I and Class II had congestive heart failure, whereas 17 of the 49 patients in Class III and Class IV presented this complication. The classification of the New York Heart Association was used: Class I: Patients with cardiac disease and no limitation of physical activity; Class II (formerly 2a): Patients with cardiac disease and slight limitation of physical activity; Class III (formerly 2b): Patients with cardiac disease and marked limitation of physical activity; Class IV: Patients with cardiac disease and who are unable to carry on any physical activity without discomfort.

A history of previous failure was likewise found to be significant. Every patient who decompensated during a previous pregnancy did so again during the observed pregnancy. However, 9 per cent of those who had never had failure before developed it during the observed pregnancy.

It has been stated that when the aortic valve is damaged the patient faces a greater risk during pregnancy than when the mitral valve alone is involved. The authors' experience does not confirm this observation. Failure was more than twice as common in patients with mitral valvular disease alone (24 per cent) than it was in those who had aortic or combined aortic and mitral valvular disease (11 per cent).

The size of the heart was determined by teleroentgenograms at several intervals during and after pregnancy in 49 patients who did not fail and in 10 who did. The maximum transverse diameter of the heart was measured and the per cent enlargement was calculated according to the table of Ungerleider and Clark (A Study of the Transverse Diameter of the Heart Silhouette with Prediction Table Based on the Teleroentgenogram, Am. Heart J., 17: 92, 1939). The weight of the patient at the time the radiogram was taken was used uncorrected when making the calculations. The results thus obtained approximated the postpartum cardiac measurements within a range of 10 per cent or less. Cardiac measurement by such a method therefore seems reliable, even though the configuration and position of the heart changes as gestation advances. None of the patients whose hearts were enlarged less than 10 per cent above normal had failure. Contrariwise, all patients who failed showed an increase of 10 per cent or more above normal. However, a number of women with 20 to 30 per cent enlargement did not experience decompensation. It was concluded from this that while patients with minimal cardiac enlargement are better risks, those with moderate enlargement are not necessarily bad risks. In so far as these limited observations indicated, there was a general but not a strict correlation between the degree of enlargement and the likelihood of failure.

Age. Patients with rheumatic cardiac disease, regardless of parity, are more prone to fail as they get older. In a group of 644 adult cardiacs (male and female), the average age of failure was 30 years. It is apparent, then, why many observers have stressed age as an important guide in the prognosis of pregnant cardiac patients. Patients above the age of 30 years, and especially above 35 years, are much more apt to decompensate than those who are younger.

Functional Class and Previous Failure. The functional capacity of the heart to do work is without doubt the most reliable single index of the prognosis in pregnancy. At times, however, it is difficult to establish this with precision and, again, it may vary from one month of pregnancy to another. An actual test of pregnancy is, therefore, more reliable; hence it is evident that a patient who has failed in a previous pregnancy will almost certainly decompensate again unless failure was due to circumstances not likely to recur, such as active rheumatic carditis (Am. J. Obst. & Gynec., **41**: 44, 1941; J. A. M. A., **91**: 1942, 1928; M. Ann. District of Columbia, **10**: 16, 1941). The contrary is not true, that patients who have not failed previously will not fail in a later pregnancy. In our series, 11 per cent of the multiparous patients who had no history of failure decompensated during the observed pregnancy.

Multiparity. Conflicting opinions have been expressed on parity: such as, the prognosis is worse in primiparas (Lancet, **1**: 629, 1935); it is worse in multiparas (J. Obst. & Gynec. Brit. Emp., **44**: 659, 1937; Edinburgh M. J., **40**: 587, 1933); parity, per se, has no important bearing on the prognosis (Am. J. Obst. & Gynec., **39**: 24, 1940; J. Obst. & Gynec. Brit. Emp., **47**: 597, 1940. This discrepancy may have resulted from the fact that the different authors did not control to the same degree, at least, 2 factors that influence the outcome, namely, the duration of heart disease (longer in multiparas) and the physical effort spent in obstetrical labor (greater in primiparas). When allowance is made for both factors, it seems reasonable to conclude that parity, per se, is of no real significance.

(This is the best article on heart disease in pregnancy that has appeared for a long time and deserves careful study by obstetricians and cardiologists alike. Despite the fact that all experienced students of the subject deprecate the use of cesarean section because of heart disease, this practice is still widely prevalent. Hence, the clear-cut statement of Bunim and Rubricius emphasizing the greater hazards of abdominal delivery in all degrees of this complication, is timely and welcome. It will be noted that 5 of the authors' patients went into failure during the last 4 weeks of pregnancy, more than in any other month. This is at variance with certain current teaching which, by emphasizing the fall in cardiac output during the last month or so, has leaned to the viewpoint that failure near term is unlikely since the peak load imposed by pregnancy is then well passed. I must say that my own experience has been in keeping with this teaching since most instances of decompensation which I have seen occurred around the 30th week rather than in the last month. However, the figures of Bunim and Rubricius make it plain that generalizations on this point are unwarranted and that the last month may be just as hazardous as any other.—Ed.)

ACUTE RHEUMATISM IN PREGNANCY

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J. Obst. & Gynaec. Brit. Emp. **55**: 50–52, February, 1948

The main purpose of this paper is to report 2 cases of pregnancy complicated by acute rheumatic heart disease. These cases are interesting in that there was no clinical evidence of the condition while the heart showed severe myocardial damage. Both patients died following delivery; in one of them the symptoms simulated acute obstetric shock. Several other cases of rheumatic heart disease in pregnancy have been reviewed and included in this report, with the purpose of determining the frequency of rheumatic recrudescences during pregnancy and the part they play, if any, in dictating the development of acute cardiac failure or the onset of decompensatoin in a heart with long standing valvular disease.

Case. 1   The patient, aged 30, was pregnant for the first time. There was no previous relevant history, and she was in good health till the onset of labor. One hour before delivery she had a rigor, and was given a pint of glucose saline intravenously. The duration of labor was 22 hours and terminated in a forceps delivery. Following delivery the blood pressure fell to 80/40, and the pulse rate increased to 140. She was given a pint of plasma, and the blood pressure rose to 105/80. Two hours later she developed acute pulmonary edema and died.

Relevant Postmortem Findings.   The heart weighed 10 ounces (283 g.). The epicardial surface was smooth, the right auricle slightly dilated, and the tricuspid valve normal. The right ventricular musculature felt flabby, and the cavity was dilated. The endocardium of the left auricle was slightly thickened and wrinkled in the region of MacCallum's patch. The mitral valve admitted 2 fingers. The cusps were thin, but showed the presence of several small verrucose vegetations along the line of closure. The left ventricular cavity was dilated, and the muscle felt somewhat soft.

The lungs showed acute pulmonary edema.

Histological Findings.   *Heart.*   The mitral valve showed slight fibrosis and infiltration by cells of the large mononuclear series. Vegetations, composed of deeply staining eosinophilic necrotic collagen, projected from the auricular surface of the cusp. In the adjacent valve spindle-shaped cells covered by a thin film of fibrin formed a palisade to the surface. In the myocardium there was paravascular scarring and in addition Aschoff nodules in all stages of development, indicating repeated recent episodes of rheumatic carditis. The coronary vessels were also involved and showed medial fibrosis and recent acute fibrinoid necrosis of their walls.

Anatomical Diagnosis.   1. Prolonged labor, maternal distress, forceps delivery. 2. Recurrent rheumatic carditis and valvulitis. 3. Acute left ventricular failure following delivery. 4. Acute pulmonary edema.

Case. 2 The patient was aged 23. It was her first pregnancy. She had a previous history of scarlet fever and rheumatic fever, but her health during the present pregnancy was excellent. The onset of labor was normal. Labor lasted for 28 hours. She was given 1 pint of glucose saline intravenously before delivery because of dehydration. Delivery was by forceps, and there was no excessive blood loss, nor evidence of shock. Nine hours after delivery, however, the patient complained of pain in the abdomen, became pulseless and died within a few minutes.

Postmortem Findings. The heart weighed 14 ounces (340 g.). The right side of the heart was normal. The left auricle was dilated, and lined by smooth endocardium. The mitral valve admitted 2 fingers, the cusps were unthickened, but along the line of closure there were small verrucose vegetations. The left ventricle was dilated, the muscle showing no macroscopic lesion.

The lungs showed terminal congestion and edema.

Histological Findings. *Heart.* The mitral valve showed the presence of numerous vessels in the auricular layer. · A vegetation with hyaline cap of collagen and Aschoff cells in its base projected from the valve surface.

In the myocardium there were numerous Aschoff nodules, all showing polarization and signs of healing. There was slight involvement of the coronary vessels and well developed paravascular scarring.

Anatomical Diagnosis. 1. Recent delivery. 2. Recurrent rheumatic carditis and valvulitis. 3. Acute myocardial failure.

Six cases of mitral stenosis in pregnancy in which the patients died from cardiac failure were examined for evidence of recent rheumatic carditis. In 4 of these rheumatic vegetations were present on mitral or aortic valves, and histologically there were Aschoff nodules of recent development, i.e., 1 to 4 months, in the myocardium. The degree of myocarditis together with the valvular lesions was such as to suggest that the recrudescence of rheumatic infection was the important factor in leading to cardiac decompensation.

One other patient died from subacute bacterial endocarditis and here again the myocardium was the site of active rheumatic lesions.

In only 1 patient with mitral stenosis and decompensation during pregnancy was there complete absence of any evidence of recent rheumatic carditis.

Comment. Most of the literature on rheumatic heart disease and pregnancy deals with the factors which determine the onset of decompensation and the prognosis is believed to depend largely on the severity of the valvular lesions. The important part played by a recrudescence of rheumatic carditis is often overlooked. The 2 cases considered in detail here illustrate that recurrent rheumatic carditis, even in a heart not the site of a mechanical lesion, may be responsible for acute myocardial failure particularly following delivery. The second group of cases shows that in mitral stenosis recurrent rheumatic carditis may often be the deciding factor which dictates the onset of decompensation, and the pregnancy itself may have little influence on the course of events.

ANTEPARTUM HEMORRHAGE

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The first section of this study reviews the cases of premature separation of the normally implanted placenta occurring in the Philadelphia Lying-In Hospital during the years 1934–1945. The group of 113 cases is composed only of those presenting one or more of the following typical clinical manifestations of placental separation: continuous uterine pain, tenseness and tenderness of the uterus, evidence of intrauterine hemorrhage, or frank external bleeding. Cases prior to the 28th week of pregnancy have been excluded.

Hypertension and/or albuminuria was found in 48 per cent of the entire group; many others presented rather typical symptoms suggestive of toxemia, and the fall in blood pressure incident to hemorrhage may have masked a hypertension in others.

The mild cases were those occurring almost always during labor, shown by somewhat more than usual bleeding, some increase in uterine tension, and occasionally, slight or moderate fetal distress. The severe cases were those in which there was evidence of a large concealed or external hemorrhage. In dealing with the milder degrees of separation occurring during labor, in which neither mother nor baby shows distress, it is rarely necessary to interfere with the normal course of labor. Of the 50 patients whose abruption occurred during labor, ¾ were delivered vaginally. Among the 47 with mild or moderate degrees of separation who were delivered by forceps, breech extraction, or spontaneously, including 9 abruptio before labor, only 1 patient died, primarily of acute hepatitis. On the other hand, the more urgent cases, because of extreme loss of blood and shock require that the uterus be emptied by the quickest method compatible with safety for the mother. Not until the uterus is empty can firm contraction close the bleeding sinuses. If the separation is of major degree and the patient cannot be immediately and safely delivered by simple measures from below, cesarean section is the treatment of choice, and in severe cases is done even though the child is known to be dead. The patient must first be treated for shock and the lost blood be adequately replaced by transfusion. A fine point of judgment is required in determining how long to postpone operative measures while awaiting reaction from shock.

The uterus was removed in only 4 of the 66 cases treated by cesarean section. Removal is done only if the uterus fails to contract following its evacuation. There was no fatality.

The likelihood of postpartum hemorrhage must be recognized. Firm packing of the uterus and vagina, and intravenous oxytocics, are urgently indicated on the least provocation.

Since 19 of the 113 babies were dead in utero at the time of admission, and since 19 of the 39 who were stillborn or died in the neonatal period weighed less than 4 pounds, the total uncorrected mortality rate of 35 per cent is better than anticipated. However, more prompt recognition of symptoms by both patient and physician could reduce the incidence. Besides the death from acute hepatitis, 1 patient died following cesarean section; it was felt that in this case shock and blood loss were inadequately treated. The maternal death rate was thus 1.8 per cent, 2 in 113 cases.

The importance of adequate prenatal care is emphasized, particularly since toxemia seems to be such a strong factor in abruptio, and where interruption of pregnancy in toxemia patients is delayed for greater viability of the child, the possibility of premature separation must be considered. Manual dilatation of the cervix and other traumatic procedures have no place in treatment of abruptio. As treatment for shock before delivery measures will decrease the operative risk, so also prompt replacement of blood following delivery decreases the immediate danger and in addition lessens the incidence of puerperal infection.

The second section of the report covers 92 cases of placenta previa during the same period—an incidence of 1 in 307 total deliveries. The study includes only those cases occurring beyond the 28th week of pregnancy in which the diagnosis was definitely established by feeling the placenta through the cervix, its visualization by x-ray studies, or by confirming its low attachment at the time of cesarean section. Of the 92, favorable factors allowed 17 to be delivered vaginally; there were no deaths. Among those treated by section, there were 2 deaths, 1 considered nonpreventable and the other attributed to inadequate treatment of shock and the use of pitocin in the induction of labor. Intrauterine asphyxia was presumably responsible for 11 of the 24 fetal deaths, and was no doubt a contributory factor in all of them; 9 of the 24 weighed less than 4 pounds.

In the management of placenta previa, accurate diagnosis of the cause of bleeding is essential. A cautiously performed vaginal examination may reveal that the bleeding is due to a cervical polyp, an erosion, or, rarely, a cervical carcinoma, rather than to a placenta previa. Examination, however, entails the danger of sudden profuse bleeding and the risk of infection, and should never be done until the operating room is ready for both vaginal and abdominal delivery. X-ray studies by the "soft tissue" technique may be a valuable aid but are dependable only in ruling out, rather than positively diagnosing, placenta previa.

Treatment of shock and replacement of blood by transfusions of whole blood or plasma are essential before instituting procedures for delivery, and in fact before digital examination, since it may start additional bleeding.

Expectant treatment of patients with placenta previa in the hope of bringing the child to greater viability is never justified unless the patient remains in the hospital throughout the remainder of pregnancy.

The method of delivery is almost wholly dependent on the status of the cervix.

Because of the danger of profuse hemorrhage from the vessels of the placental site and the added risk of infection, manual dilatation of the cervix and forcible vaginal delivery have no place in the treatment of this condition. If the cervix is dilated and the placenta previa is only partial or marginal, rupture of the membranes will allow the presenting part to make pressure on the placenta sufficient to stop the hemorrhage. Under similar conditions version and extraction are indicated only if the cervix is *completely* dilated. Braxton Hicks version should be utilized only in those cases in which the baby is dead or nonviable and in which the cervix is partially dilated; in emergency it may save the mother's life but it almost certainly sacrifices the child. The authors no longer use the hydrostatic bag, after several instances of continuing intrauterine hemorrhage following its insertion.

In all cases in which the cervix is not dilated, in all cases of central placenta previa regardless of the cervical dilatation, and in those of malpresentation of the fetus, cesarean section is the safest, and therefore the most conservative form of treatment.

The use of an oxytocic intravenously immediately on completion of the second stage of labor, and firm packing of the uterus and the vagina after expulsion or removal of the placenta will considerably lessen the danger of postpartum hemorrhage. In most instances packing the uterus after cesarean section for placenta previa is advisable. Blood transfusions are indicated following delivery to combat anemia and to improve the patient's resistance to infection. 16 tables.

(This paper, which is based on the experience of one of our leading clinics, surveys con⁴ cisely and with sane judgment the two main causes of hemorrhage in the last trimester o pregnancy. Those who still hold to vaginal delivery in premature separation of the placenta as the procedure of choice for all, or almost all, cases of this complication, will not approve of the 58 per cent frequency of cesarean section, but I agree with the authors to the extent that full justice cannot be done these patients without a substantial employment of abdominal delivery. As I see it, the main injunction in this conditoin is to deliver the patients fairly promptly by whatever means is simplest. If the patient is already in labor and progressing satisfactorily, the simplest method is vaginal delivery since, under these circumstances, delivery can usually be anticipated fairly promptly, that is, within a few hours. On the other hand, if labor has not set in and the cervix is closed and uneffaced, the simplest (as well as the most conservative) method of effecting prompt delivery is cesarean section. This seems only common sense and I believe that the great majority of obstetricians will agree.

Our policy in the management of premature separation of the placenta at the Johns Hopkins Hospital (at least in regard to cesarean section) appears to have been quite constant since the inception of the obstetrical department in 1896. Thus, in the last 15 years, our incidence of abdominal delivery in premature separation has been 28.6 per cent, while for the entire 52 year period it was 27.1 per cent. This general policy, applied to more than 300 cases dating back to 1896, has resulted in a total of 7 maternal deaths. In the last 20 years, in the course of over 125 cases, only 1 mother died,—a patient who was admitted in critical condition and died before any form of therapy could be instituted. This mortality experience is of the same order as that reported by Kimbrough and Jones. While these data support plainly the judicious employment of cesarean section in premature separation of the placenta, it is also true that the prompt and liberal use of blood transfusions is a more important factor in determining maternal outcome in this condition than is the type of

delivery. Thus, if one had the alternatives of delivering a series of cases vaginally *with* blood transfusions, or abdominally *without* transfusions, it would require only a few moments' reflection to choose the former.

The authors report a fetal mortality of only 35 per cent and when corrected for premature deaths, this becomes 21 per cent. The gross figure of 35 per cent is extremely low in comparison to the 60 to 90 per cent usually reported and is especially remarkable in this particular complication which, by definition, is instantly fatal to the baby unless it happens to be minor or moderate in degree. The cases in the above paper were included on the basis of clinical findings only, that is, on 1 or more of the following typical manifestations of placental separation: Continuous uterine pain, tenseness and tenderness of the uterus, evidence of intrauterine hemorrhage, or frank external bleeding. This brings up the question (and Kimbrough and Jones themselves raise it) as to the criteria upon which the diagnosis of premature separation of the normally implanted placenta is justifiable. In outright cases showing both clinical and placental evidence of the accident, this is of course easy, but what about the case in which there is certain clinical evidence of premature separation, but no placental sign, or conversely, the case in which there are small retroplacental clots but no clinical evidence? The great majority of true cases of premature separation of the placenta show both clinical and placental signs of the accident; and it would be my reaction that both sorts of evidence (to some degree at least) should be demanded as criteria for diagnosis if our analyses of this group of cases are to be uniform and valid.

By way of illustrating the desirability of careful placental examination in establishing the diagnosis of placental detachment, let us consider a condition which is almost invariably mistaken for classical separation, namely, rupture of the marginal sinus of the placenta. A number of such cases happen to have come my way in the past few years and there can be no question that they simulate mild cases of premature separation of the placenta very closely. Uterine pain and tenderness, however, are usually moderate and shock is rare. Fetal death in utero occurs, uterine tenseness and vaginal bleeding develop and blood clots come out with the placenta. The placenta, however, may show no signs of detachment at any point, but does reveal an easily demonstrable rupture of the marginal sinus if it be looked for. All series of cases of premature separation of the placenta hitherto reported (including our own 300 mentioned above), undoubtedly include a substantial number of these sinus ruptures for they are by no means rare.

Bearing also on the problem of valid diagnosis in this condition is the fact that, as it occurs earlier and earlier in pregnancy, it partakes more and more of the picture of a late abortion. Indeed, if the complication occurs at the 26th week, we call it an abortion, but if it takes place 3 or 4 weeks later, it is designated as premature separation. This is justifiable in general on the grounds that this accident in late pregnancy is associated with a number of grave phenomena which are not seen in placental detachment during the first two trimesters and which call for some special name and consideration. But to draw the line sharply at the 28th week between abortion and premature separation puts most cases which are on the immediate side of this dividing line in a very questionable status from a diagnostic viewpoint. This is especially true on the upper side, for most cases of so called premature separation of the placenta between the 28th and 32nd week resemble late abortions more than they do detachment. From the viewpoint of management, furthermore, it should be noted that the signs and symptoms in these earlier cases rarely call for cesarean section.

In sum, premature separation of the placenta, in its milder forms, is not as clearcut an entity as we may have been inclined to believe, and as a consequence, statistical analyses of this group of cases must be evaluated with caution.

In regard to placenta previa, the authors find this complication somewhat less frequent (1 in 307 cases) than premature separation of the normally implanted placenta (1 in 250 cases). This is contrary to our experience which shows placenta previa at least twice as common, but this discrepancy is probably but another example of lack of uniformity in the diagnosis of premature separation. The authors' incidence of cesarean section in placenta

previa, namely, 81 per cent, is of the same order as that in our own clinic where abdominal delivery is used in about 60 per cent of cases. Having been brought up on the bag and Braxton Hicks' version in placenta previa and having seen my share of fatal lacerations of the cervix from their use, I have reason to believe that these measures have no place in the modern management of this complication and that cesarean section must be employed in some such incidence as mentioned above if deaths from this condition are to be kept to a minimum.—Ed.)

THE EXPECTANT MANAGEMENT OF PLACENTA PREVIA

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Am. J. Obst. & Gynec., 55: 169–176, Jan. 1948

While maternal mortality has been appreciably reduced in the past decade, mainly by whole blood transfusions to replace blood loss, fetal mortality in placenta previa remains high, largely because of prematurity. Ample, properly matched blood and caution in the use of vaginal manipulations may make it possible to continue the pregnancy until the child is larger and so increase the fetal salvage.

Among 105 cases of placenta previa seen during the past 11 years, 41 were treated in an expectant manner. Of the total cases, 21 were classified as central, 23 as partial, and 61 as marginal. Diagnosis was established on cesarean section or on vaginal examination. Diagnosis by x-ray examination was attempted in 64 patients, with positive diagnosis for placenta previa in 51 and inconclusive findings in 13.

There was one maternal death (0.95 per cent), a multipara in her 8th month of pregnancy with a dead fetus. There had been persistent bleeding at home for 3 weeks, and numerous vaginal examinations by the local physician, following 1 of which an alarming hemorrhage occurred. Patient arrived at the hospital almost exsanguinated and with a temperature of 101°F. Five days after an easy delivery induced by rupture of membranes she died of a generalized infection (before the era of chemotherapy).

The fetal mortality was 28 per cent—14 stillbirths and 15 neonatal deaths among 105 infants. Among the 74 patients who were successfully carried to term or who did not have their initial bleeding until the child was of term size, the fetal mortality rate was only 10 per cent, as compared with a rate of 68 per cent in the 31 patients who went into labor spontaneously or in whom the pregnancy was terminated before the child attained a size of 2500 gm. Recent reports in the literature average about 32.5 per cent fetal mortality, while the earlier methods resulted in 5–10 per cent maternal deaths and 40–60 per cent fetal deaths.

In treatment of antepartum bleeding, ample properly matched blood should

be given. Placenta previa requires hospitalization for diagnosis and treatment. Vaginal examinations performed in the home may cause more hemorrhage, occasionally seem to start uterine contractions, and in general do not improve the outlook for mother or baby. In addition, vaginal examinations, particularly if packing is placed in the vagina and around the cervix, carry the risk of infection.

Usually the presenting part does not engage satisfactorily in the superior strait of the pelvis, as may be determined by abdominal examination, if any appreciable degree of placenta previa is present. The high unengaged presenting part or an abnormal presentation, transverse or oblique, in the presence of antepartum bleeding, strongly suggests placenta previa.

If the patient is at term or has an apparently viable baby, a method of delivery may be selected as soon as her condition permits. If the presenting part is not engaging in the pelvis, vaginal examination is particularly hazardous and is often omitted. When delivery is decided upon, if the part is still floating or presenting abnormally, cesarean section is done. Even though the preoperative diagnosis may at times be incorrect and the bleeding from another cause, it is felt that an abnormal presentation with a viable baby is more safely delivered by section.

If the presenting part is dipping into the pelvis and delivery has been decided upon, a vaginal examination is done. The condition of the cervix and lower segment is gently determined. When the presenting part cannot be readily felt through the tissues lateral to the cervix, it suggests the presence of placental tissue in the lower segment. If the cervical canal is short and admits the finger, the region around the internal os is cautiously felt. If placental tissue is palpated, every effort is made to avoid disturbing its attachments. If the cervix is short, soft, and patulous, and a portion of the internal os is not covered by the placenta, the membranes are ruptured. When the cervix is not favorable for vaginal delivery, or if the internal os is completely covered by placental tissue, cesarean section is performed.

Where the child seems too small to survive and labor has not begun, a gentle examination of the vagina and cervix may be done to eliminate the possibility of bleeding from ruptured varices or cervical tumors, but the cervical canal should not be explored. The patients are kept under observation, preferably in the hospital, although some have been allowed to go home under instructions to abstain from sexual intercourse, to permit no vaginal examinations, and to return to the hospital with the 1st recurrence of bleeding. Forty-one patients were kept under observation, from 2 days to 3 months, in an effort to obtain a viable child; 14 had 2 or more periods of hospitalization for recurrent bleeding. Of these 41, 5 babies (12 per cent) were lost: 1 term baby with congenital malformations, 1 stillborn premature, and 3 prematures who died neonatally. In view of the better fetal results (12 per cent mortality as compared with 28 per cent for the entire series) and with no apparent increased maternal risk, it would seem that an expectant attitude in the management of placenta previa is worthy of trial.

Although one discussant believed that those who are kept under observation for either ectopic pregnancy or placenta previa can sustain major hemorrhage and reach irreversible shock before they can be helped, and that consequently in

cases of placenta previa the pregnancy should be terminated irrespective of the estimated age of the fetus, the majority of the discussants agreed that expectant treatment is of value in certain cases, provided always that the patient is kept in a hospital adequately prepared to meet any emergency and always under trained observation. 5 tables.

(This is presumably the last article of the late Tiffany Johns Williams, for many years Professor of Obstetrics and Gynecology at the University of Virginia. Like his other contributions to the literature, it is a well balanced and judicial study of a timely topic. He will be sorely missed as a teacher, clinician and friend.—Ed.)

THE FATE OF THE LIVING VIABLE BABIES IN EXTRAUTERINE PREGNANCIES

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A report of 316 living viable babies in extrauterine pregnancies, in a review of the world literature in 1935, disclosed that a statement of development was made in only 64 cases, and of these, 46.6 per cent were deformed. Of the 44.3 per cent that survived for 8 days or more, development was reported in 41 cases, 36.6 per cent deformed. According to another review in 1938, 57.1 per cent of 266 living, viable babies survived 8 days or more, and 10.5 per cent were recorded as being deformed. A review of 106 cases in 1938 found development mentioned in only 82; of these, 39 per cent were reported deformed. As reviewed in 1942, of 179 extrauterine pregnancies of more than 5 months' gestation, only 23.5 per cent delivered living, viable babies. A specific statement of development was made in 13 cases, of which 10 were deformed. A report of 20 abdominal pregnancies at Charity Hospital in New Orleans indicated that only 15 per cent delivered living viable babies. According to Winkel, 75 per cent of the deformities include the head, $\frac{1}{2}$ of them the lower extremities, and 40 per cent the upper extremities.

The present authors review 41 additional cases in the literature. Among 31 of these, 38.7 per cent were found to be deformed. Four new cases of extrauterine pregnancy with living, viable babies are reported. While 1 child presented a plastic deformity of the head, a right club foot, and contraction deformities, yet survived and was last seen at 5 months, 2 were deformed and died within 24 hours. The 4th child was apparently normal but died within a few minutes.

It was concluded that only about $\frac{1}{4}$ of the extrauterine pregnancies diagnosed

after the 5th month will result in living, viable babies. About $\frac{1}{3}$ of the living, viable babies will have deformities, and about $\frac{1}{2}$ of the living, viable babies will survive 8 days or more. 1 table.

LEUCORRHOEA IN PREGNANCY (A FURTHER STUDY WITH SPECIAL REFERENCE TO THE HYDROGEN ION CONCENTRATION AND LACTIC ACID CONTENT OF THE VAGINA).

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In cooperation with
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It is well known that the reaction of the vagina during the period from puberty to the menopause is definitely acid, the normal pH being in the range 3.8–4.4. Various workers have shown that lactic acid is present and Cruickshank (J. Path. Bact., 39: 213, 1934) has suggested that this lactic acid is very probably produced from glycogen, present in the vaginal epithelium, by Doderlein's bacillus which is normally the preponderating organism in the adult human vagina. It has also been demonstrated that, when the vagina is infected with certain other organisms, the pH is usually high; for example, in cases of vaginal thrush the average value is 4.8 (Liston, W. G., and Cruickshank, L. G., Edinburgh M. J., 47: 369, 1940b), while in trichomonas infestations it is 5.34 (Liston, W. G., Brit. J. ven. Dis., 16: 113, 1940). The normal high acidity of the vagina evidently aids greatly in preventing the multiplication of the harmful organisms. Though the importance of lactic acid in the vagina has been widely recognized, few attempts seem to have been made to determine quantitatively the concentration present.

The object of the present investigation has been to obtain data concerning the pH and the lactic acid content of the vagina from a number of patients. In this way it was hoped to obtain information as to how far the pH is determined by the concentration of lactic acid present. Cytological and clinical observations were also made so that variations in lactic acid and the pH could be correlated with these findings.

The result of the study of this series of 200 cases of leucorrhea in pregnant women very closely conforms to the findings obtained in the first series of similar cases which has already been published in this Journal (Liston, W. G., and Cruickshank, L. G., J. Obst. & Gynaec. Brit. Emp., 47: 109, 1940a). The vaginal contents of a normal pregnant woman present the following characteristics:

(1) Desquamated epithelial cells are more numerous than pus cells. (2) The epithelial cells are loaded with glycogen. (3) The bacterial flora consists of an

almost pure culture of Doderlein's bacillus, i.e. Type I flora. (4) The acidity of the vaginal contents measured as pH varies between 3.8 and 4.4. (5) The concentration of lactic acid in the discharge has a mean value of 0.032 M. (mols. per liter).

Closely resembling the normal condition are certain cases which show a small erosion of the cervix. Those cases, so far as the contents of the vagina are concerned, can be distinguished from the normal by the presence of a larger number of pus cells, slightly less glycogen in the epithelial cells, a bacterial flora with a few rather smaller gram-positive bacilli than Doderlein's organism, i.e. a bacterial flora of Type II, a less acid state of the vagina indicated by a rise in the pH to 4.42 and a decrease in the concentration of lactic acid to 0.030 M. As the size and extent of the erosion of the cervix increases the abnormal features of the vaginal contents noted above become more and more accentuated until in cases with very large erosions pus cells become much more numerous than the epithelial cells in the discharge, and at the same time the discharge becomes more abundant. Such desquamated epithelial cells as are present in the discharge are found to contain less glycogen. Red-blood cells may also be present. The bacterial flora becomes even more mixed, gram-negative organisms of various kinds now preponderate and the bacterial flora passes gradually through II to Type III. The pH rises in medium erosions to 4.64 and in large erosions to 5.32. The lactic acid concentration falls considerably—to 0.022 M. in medium erosions, to 0.018 M. in large erosions.

Patients suffering from vaginal thrush constitute about 25 per cent of the cases of leucorrhea in pregnant women. The condition is easily recognized by finding the pseudo-mycelium or the blastospores of the fungus. The leucorrhea of thrush may be uncomplicated or it may be associated either with an erosion of the cervix or with the presence of T. vaginalis in the vagina. In 27 uncomplicated cases the pH was found to be 4.63; this figure is the mean of 61 examinations. The lactic acid concentration in uncomplicated thrush estimated in 39 samples gave a mean concentration of 0.026 M. When thrush is associated with an erosion of the cervix, or with the presence of T. vaginalis in the vagina, the pH rises, in the former case a mean pH of 4.72 was obtained as the result of the examination of 19 samples and in the latter case a mean pH of 4.93 based on 47 examinations. The concentration of lactic acid also decreases to a mean of 0.019 M. when thrush is associated with a cervical erosion and to a mean of 0.025 when associated with Trichomonas vaginalis; those figures are based on 7 and 23 examinations respectively.

The commonest cause of leucorrhea in pregnant women is the infestation of the vagina by the parasite Trichomonas vaginalis. Among the 200 women at present under consideration, T. vaginalis was found in the vagina in approximately 40 per cent. Trichomonas vaginalis may be found alone or it may be associated with erosions of the cervix or with the fungus which causes thrush. In uncomplicated Trichomonas infestation the vaginal contents have a pH reaction of 5.11. This is the mean figure of 161 examinations in 63 patients. The lactic acid concentration in 106 examinations gave a mean figure of 0.020 M. When the

thrush parasite complicated the presence of T. vaginalis the contents of the vagina were slightly more acid, yielding a mean pH reaction of 4.93 in 47 examinations; the lactic acid concentration being then 0.025 M., the mean of 23 examinations.

When Trichomonas infestation was combined with a cervical erosion, a less common complication than with a thrush infection, these cases showed a less acid reaction, a pH of 5.58, the mean of 12 examinations. In the same circumstances the concentration of lactic acid was also lower, 0.015 M. being found as the mean of 7 examinations.

Apparently T. vaginalis lives upon glycogen and flourishes in a slightly acid medium, the most favorable pH being around 5.3. Such conditions are found in the vagina of certain women in whom the amount of glycogen in the epithelial cells is less abundantly present in that situation than normal, and in consequence these cases show a rather higher pH reaction than normal.

Trichomonas vaginalis often disappears from the vagina after labor and may not be found there for some time, but, in the end, after some weeks, or months, it appears again in the vagina when the conditions become favorable for its multiplication.

Girls, before puberty, are not subject to infestation with T. vaginalis. It is generally believed that until puberty the reaction of the vagina is not acid nor is glycogen then present in the epithelial cells. It is the absence of glycogen, the food on which this parasite lives, which is probably the most important factor in preventing the growth and multiplication of this parasite in the young female.

At birth glycogen is abundantly present in the epithelium of the vagina but during the course of the first and second week of life this glycogen-charged epithelium is desquamated and is discharged from the vagina. It has been argued from this fact that the presence of glycogen in the epithelium of the vagina in the newborn infant is the result of the action of a hormone derived from the mother which is transferred to the infant before birth through the placenta and that it is the absence of this hormone in the infant after birth which causes a halt to the deposition of glycogen in the epithelial cells. At the age of puberty, however, when the young female can produce the hormone herself, the deposition of glycogen in the epithelial cells of the vagina is restored and then conditions become suitable for the parasite Trichomonas vaginalis.

Shortly after parturition the pH of the vaginal contents rises to a point around 6. Glycogen is practically absent from the epithelial cells and the T. L. is very low (average values 0.006 M.). Conditions then are no longer suitable for the growth and development of T. vaginalis or O. albicans; the symptoms due to these parasites consequently disappear. When, however, the acid state of the vagina returns, cases which previously showed T. vaginalis often relapse and the organisms reappear in numbers in the vagina. On the other hand, O. albicans often disappears permanently after parturition, especially when glycosuria comes to an end.

A CLINICAL AND HISTOPATHOLOGIC STUDY OF LESIONS OF THE CERVIX UTERI DURING PREGNANCY

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Am. J. Obst. & Gynec., 55: 133–150, Jan. 1948

The study is based on the examination of tissues obtained from the cervix uteri of 89 patients at various stages of gestation. Four were obtained by hysterectomy and the others by removal of a lesion recognized grossly or by a biopsy of the cervix.

Gross and histopathologic examination showed mucous polyps of the cervix in 37, erosion of the cervix in 32, carcinoma of the cervix in 10, condyloma acuminata in 5, endometrial polyps in 3 and leucoplakia in 2. The age distribution was fairly even between 18 and 41 years except for the cancer patients where the majority fell in the late 30's.

There are a great many papers dealing with the gross and histologic changes in the cervix uteri during pregnancy, mostly with the formation of the lower uterine segment or with cervical dilatation during labor. The generally accepted description of the cervix during gestation is that of Stieve (Ztchr. f. Microskop. Anat. Forsch., 11: 291, 1927). According to Stieve, there is during the premenstruum an enlargement and increased secretion of the cells of the cervical glands which is preliminary to the transformations occurring during gestation. In the first $2\frac{1}{2}$ months, however, the most prominent changes are in the connective tissue elements, the fibrous tissue cells, of which the cervix is mostly composed, increasing in size and number. Though the muscle plays a secondary role, its cells also hypertrophy, reaching a maximum about the third month. The most striking finding at this early stage is a tremendous increase in the number of blood vessels and lymphatics; this continues throughout pregnancy, the cervix eventually becoming a soft boggy structure comparable to "erectile tissue." Leucocytes, wandering cells, and plasma cells invade the mucosa. Stieve failed to find clear evidence of decidua formation, but others have reported islands of decidualike cells.

The individual cells of the cervical glands increase in height, proliferate, and produce a marked amount of mucus progressively throughout pregnancy. After the 12th week the glands increase in number, invade the substance of the cervix and project into the cervical canal; they measure 4–6 mm. compared with an average depth of 1–2 mm. in the non-pregnant cervix. A marked increase thus appears in the radial measurement of the cervix, half of which is now composed of mucosa. The extension of the glands into the cervical lumen throws the mucosa into manifold folds which form the *arbor vitae*, having a honeycomblike appearance with many projections into the cervical canal.

To obtain some data on the occurrence of so-called cervical erosion during pregnancy, a series of 119 consecutive private patients was analyzed. At the

first prenatal visit an erosion was observed in 48 per cent, with little difference between primigravidae and multigravidae, and with an increase in number among those first seen after 12 weeks as compared with those seen earlier. Of 79 patients seen both before and after delivery, 55 per cent had this lesion 6–8 weeks post partum.

A cervical erosion is essentially a very shallow ulcer with fairly clear-cut edges. It may be a circular lesion 1–2 cm. in depth about the external os, may occupy a small segment, or may extend far up the portio vaginalis. The base may be smooth or have a granular appearance. When there is a concomitant infection, Nabothian follicles stand out as small yellow points. Its flaming red color, especially pronounced when the vaginal mucosa assumes the typical deep purplish hue of pregnancy, is characteristic. It usually bleeds readily on the slightest manipulation.

A diagnosis of erosion of the cervix, based on both clinical and histopathologic features was made in 32 patients in this series; in 19 there were no associated symptoms, in 6 bleeding, in 5 "spotting" or a blood-tinged discharge, and in 2 an undue white discharge.

Histologic examination showed a wide variety of changes. (a) Adenomatous proliferation of the glands is the most striking change and probably the basic structure. The living cells, of a very high cylindrical type, increase so much that they often become stratified and form small projections into the lumina of the glands. The glands increase greatly in number and interspersed among those with this type of epithelium may be found many distended cystic structures with the living cells of the low cuboidal variety. These glandular formations are seen not only at the surface but even to a depth of 6–8 mm. in the substance of the cervix. The covering epithelium of high cylindrical cells may also alternate with patches of squamous epithelium. This adenomatous process appeared in 24 of the 32, intense cervicitis occurring only 5 times and a moderate infiltration with leucocytes, plasma cells and histiocytes in 1. There were accompanying papillary outgrowths in 10, hypertrophy of the squamous epithelium in 2, and hyperactivity of the basal cells or epidermidization in 6. In 6 cases islands of decidualike cells were seen. In 2 biopsies no glandular elements were seen but cervicitis, moderate round cell infiltration, hypertrophied squamous epithelium, and islands of decidua occurred in 1 or both.

(b) The second characteristic feature involving the cylindrical epithelium was an extensive papillary outgrowth, generally attributed to a hyperplasia of the connective tissue, found predominantly in 6 of the 32 cases. Extensive cervicitis was present in 3, round cell infiltration in 4, hypertrophied squamous epithelium once, and islands of decidua in 3.

(c) Edema and increased vascularity were particularly in evidence in all instances.

(d) Infiltration with inflammatory cells is of importance because of the prevalent concept that all erosions should be considered the result of infection. However, a marked cervicitis could be found in only 9, and moderate infiltration of leucocytes, plasma cells and histiocytes in 12 cases. This is contradictory to

Stieve who reported such wandering cells as a constant finding in the normal cervix.

(e) The occurrence of a hyperactivity of the basal cell layers of the squamous epithelium and of epidermidization is especially important in view of the search for methods dealing with the recognition of early carcinomatous changes. An excessive hypertrophy was seen in 4 cases of this series; epidermidization or hyperactive basal cells appeared in 6 cases, all in the group characterized by adenomatous proliferation of the glands.

When epidermidization occurs the cylindrical epithelium is found undermined by developing basal cells. These proliferate, become stratified, undergo vacuolation, and gradually displace the cells at the surface. The individual cells stain evenly, do not show undue variations in size and mitoses are infrequent. In basal-cell hyperactivity an already developed squamous epithelium sends out shoots containing immature rapidly proliferating cells which stain irregularly. There may be considerable variation in the size of the individual cells, and many mitotic figures can be found. It is this picture which presents a difficult problem in differentiation from an early carcinoma.

(f) Extensive transformation of the stroma into decidua was noted only once, but isolated islands of decidua were noted in 11 instances.

These observations suggest that most of the cervical erosions seen during gestation are not the result of a cervicitis but are a type of adenoma. Several points may be emphasized: (1) in a small series, half the patients had a cervical erosion at some time during pregnancy, a proportion too great for the normal female population; (2) only $\frac{1}{3}$ of those seen during the first 12 weeks but 59 per cent of those seen later had such lesions, suggesting that erosions appear at about the same time that maximum normal proliferation of the mucosa occurs; (3) histologic examinations of 32 erosions showed an extensive cervicitis in only 9.

The largest group, 37, in this series of 89 cases, was of mucous polyps originating from the external os or from the cervical canal. Bleeding occurred in only 6 instances. Histologic findings closely resembled those found in erosions, except that extensive inflammatory processes were more frequent (17 of 37), while moderate infiltration was noted 6 times; the formation of decidua was much more marked; and epidermidization and basal-cell hyperactivity were observed in 6 cases. Some of these polyps may have been of endometrial origin.

In 13 instances the polyp was essentially an adenoma. Ten were papillary offshoots found with cervical erosions. A moderate proliferation of glandular elements, scarcely more than expected in a normal cervix, was noted 7 times. No glands were seen in 7 sections, composed mostly of a core of connective tissue and some muscle cells, with a surface epithelium; extensive decidua formation was demonstrable in 6 of these, marked inflammation in 5 and necrosis in several.

Three polyps were classified as endometrial on basis of the facts that they were composed almost entirely of decidua and the individual cells were larger and stained more regularly and deeply than those of the normal cervical polyps, and that the few glands present resembled glands from the isthmus rather than the usual cervical type.

Carcinoma was found in 10 cases, 6 of which were reported in 1934 (Emge, Am. J. Ob. & Gynec. **28**: 682, 1934). The 4 additional cases were all diagnosed as operable. One with an immature squamous cell carcinoma has survived 6 years after treatment with both radium and hysterectomy. Another died of a gas bacillus infection following a first radium application, given at the County Hospital. The other 2 are very recent patients, 1 undergoing a laparotomy for ectopic pregnancy and radium therapy and the other a hysterectomy and radium therapy.

One discussant stated that it seems the increase in bulk of the tissues can account for cervical erosion during pregnancy by simple eversion of the excess tissue through the external os; an endometrial implant on the mucous membranes is another condition which may occur. Another pointed out the possible influence of hormones on the squamous epithelium, the need for studies of biopsies or surface scrapings at various points in the cycle, and the practical fact that erosions and polyps are a not uncommon cause of bleeding (which many women may report as menstruation) during pregnancy. The rapidity of changes in the cervix and the role that lacerations may play in distorting the appearance were emphasized. Others questioned the use of the term "erosion" and also spoke of the similarity of some of the demonstrated material to the commonly observed circumostial vermilion zone. 2 tables, 13 figures.

(Current reports on carcinoma in situ have aroused new interest in the physiological changes which the cervix undergoes in pregnancy and their similarity to malignant alterations. In Fluhmann's 89 cases, epidermization or hyperactive basal cells appeared in 6 instances. In basal cell hyperactivity, he points out, an already developed squamous epithelium sends out shoots containing immature, rapidly proliferating cells which stain irregularly. There may be considerable variation in the size of the individual cells and many mitotic figures can be found. "It is this picture," he concludes, "which presents a difficult problem in differentiation from an early carcinoma".

A similar study published by Hofbauer in 1933 revealed comparable findings (Am. J. Obstet., & Gynec.: *25*, 779, 1933). In the routine examination of 29 cervices of gravid uteri, the following changes were encountered in 8: epithelial proliferation with stratification; occurrence of mitotic figures in the proliferating epithelium; considerable epithelial downgrowth into the connective tissue; indirect metaplasia; and goblet cell formation. "Occasionally the amount of such epithelial downgrowth into the stroma may be extreme," he continues. "Under these conditions, the proliferation may cause resemblance to malignant disease."

The physiological alterations described above have recently become an especial source of confusion and uncertainty because of current efforts to make the diagnosis of cervical carcinoma earlier and earlier on the basis of microscopic findings. A growing number of obstetricians and gynecologists are sending to pathologists doubtful cervical biopsies from pregnant patients asking if the diagnosis be true carcinoma. Some of these women have been subjected to radical treatment simply on the grounds of the microscopic picture. In one questionable case in our own clinic, slides were sent to 3 gynecological pathologists of national renown: one called the lesion carcinoma in situ, one stated it was invasive carcinoma, while the third regarded it as benign. In the very next abstract a case is reviewed in which the pathological reports were similarly inconsistent.

In view of all this it seems evident that the diagnosis of early carcinoma of the cervix in pregnancy must be made with great hesitation unless there is gross as well as microscopic evidence of malignancy. In cases in which the evidence is solely microscopic, the patient

should of course be carefully followed with subsequent biopsies, but watchful waiting is the program of choice in the great majority of these cases.—Ed.)

GROSS HYPERTROPHY OF THE PREGNANT UTERINE CERVIX SIMULATING CANCER

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This case is recorded because no description of anything like it has been found in the standard textbooks and, while expert pathological advice was unable to find any exact solution of its histological problem and the description is thus somewhat inconclusive, it is possible that similar cases may be brought to light and the condition accurately determined.

CASE RECORD

History. A woman, aged 26, was seen in consultation on February 22, 1946, because of an unusual appearance of the cervix uteri, coupled with a blood-stained discharge, in the 36th week of pregnancy. She had had one normal previous pregnancy—which had resulted in the birth of a healthy boy in 1944. The 2nd child was due on March 20, 1946.

Examination. Vaginal examination disclosed no abnormality of the bony pelvis and no unnatural hardness could be determined in the cervix, although its outline was definitely irregular. Viewed through a speculum, however, the cervix was grossly hypertrophied, showed numerous areas of ulceration exuding purulent material and bled freely at the lightest touch. Indeed, on excising a piece for biopsy, bleeding was brisk enough to require vaginal plugging.

Diagnosis. A tentative diagnosis of cervical cancer was made on these clinical findings and the woman was admitted to the hospital forthwith for further investigation and treatment.

Progress and Treatment. There was no fever and no further bleeding occurred when the vaginal plug was removed after 24 hours, although there was a markedly offensive discharge which increased daily in quantity. X-ray examination confirmed the presentation of the fetus and disclosed no other abnormality. The Wassermann reaction and gonococcal fixation tests were negative, as were attempts to demonstrate the gonococcus by smear and culture. The blood count was normal.

Dr. Gleave, pathologist to the Royal South Hants Hospital, reported on the cervical fragment as showing gross hypertrophy unlike anything he had seen previously, but no clear-cut evidence of malignancy.

Operation. On February 28th, under nitrous oxide and oxygen anesthesia, the

cervix was again exposed with a speculum and was found to present a remarkable condition of septic hypertrophy so that the whole of the upper vagina was filled with an exuberant mass, oozing pus from many crevices and bleeding freely when touched.

A fragment as large as a sugar lump was excised before the vagina was packed, but, from the enormous increase in size of the mass in the 6 days since first examined, the presence of a neoplasm seemed certain and the risk of malignancy great enough to justify terminating the pregnancy forthwith by abdominal section.

Accordingly, cesarean section was performed through a midline subumbilical incision, a classical uterine incision being preferred because of the possibility of neoplastic involvement of the lower segment. Ether was added to the gas mixture to procure sufficient depth of anesthesia and there was moderate cyanosis of the child at birth. This, however, a male weighing $5\frac{3}{4}$ pounds, soon recovered and showed no defect. The placenta was normal in appearance and insertion and bleeding was slight. No invasion of uterine body, parametrium or glands was detected.

Puerperium. As unequivocal evidence of malignancy was confidently expected from the second biopsy, it seemed wise to avoid lactation and Stilbestrol 5 mg. daily for 10 days was given to the mother, together with a course of sulfathiazole amounting to 25 gm. This last was given with the object both of minimizing the evident risk of intrauterine infection and also as far as possible to clear up the septic element of the cervical lesion preparatory to irradiation. Further smears and culture at this stage revealed a mixed vaginal flora with no evidence of hemolytic streptococci or gonococci.

Clinically, the puerperium was uneventful and there were no postoperative complications. Indeed, it was the obvious well-being of the patient and the rapid decrease of the discharge (even allowing for the effects of sulfathiazole) that instilled the first doubts as to the accuracy of the diagnosis. The pathological reports completed the dilemma.

Pathology. Dr. Gleave, reporting on the 2nd biopsy fragment, again commented upon the remarkable degree of hypertrophy and said that in his opinion the condition was malignant, but, as there were unusual histological features, he would welcome other opinions. Through the good offices of the Pathological Advisory Committee, 3 eminent pathologists kindly examined the sections and a transcription of their reports is given.

PATHOLOGICAL REPORTS

Professor M. J. Stewart. "This section shows very notable proliferative activity of both endocervical and squamous portions of cervix, but especially the latter. It is well differentiated squamous epithelium, but very active indeed, containing in places mitotic figures in large numbers. There is also very notable intermingling of squamous and glandular tissue due, I should say, to downgrowth of the squamous element, since many of the glands are apparently stretched out as a result of this overgrowth. Abundant signs of inflammatory change are pres-

ent, including collections of pus, both within the lumen of some of the endocervical glands and also in relation to some of the squamous epithelium, while the stroma generally shows patchy infiltration by plasma cells and lymphocytes. I imagine that the existence of pregnancy may have a stimulating effect on proliferative activity in the cervix as elsewhere, but I am bound to say I think the squamous epithelial overgrowth here is not mere metaplasia, but neoplastic. Admittedly, there is direct continuity between the squamous epithelium and the glandular at many places, such as one sees in squamous metaplasia, but there is far greater evidence of proliferative activity in the squamous epithelium than I have ever seen in metaplasia. In addition, much of the deeper squamous tissue is irregular and the edge (stratum germinativum) is also irregular at many points. The most favorable aspect is the massive character of the proliferation, without small cell-groups infiltrating deeply beyond the general edge. Therefore, although I think the condition is most probably malignant, it is certainly not of the infiltrative type; but, as I say, I have no experience of the effect of pregnancy on the portio vaginalis cervicis."

Professor D. F. Cappell. "I do not think the cervix is the seat of malignant disease. There is quite an unusual amount of proliferation and thickening of the squamous-epithelial covering, and also, I think, an increase of the cervical mucous glands with abundant inflammatory infiltration. I do not feel satisfied, however, that the condition is neoplastic. The thickening of the epithelium reminds me of what one sometimes sees in the so-called "venereal warts" in spite of the negative G.C.F.T. I wonder if this could be an infection of the cervix with the papilloma virus which seems to be responsible for that condition."

Professor J. H. Dible. "The section shows cervicitis, infection and marked squamous overgrowth and replacement of cervical glandular epithelium. There ·is hyperkeratiasis and a quasi-polypoid overgrowth of cervical epithelium. I have never seen an exactly similar condition as far as I can remember. I can find no definite evidence of malignancy; the polymorph invasion of squamous epithelium is, perhaps, a little suspicious. I think in this case the clinical condition should be an important guide in view of the unusual and rather equivocal histological findings. In any case, the patient should be watched."

Subsequent Progress. Detailed re-examination of the cervix on March 21, 1946, 3 weeks after operation, revealed rapid healing. The cervix was reduced to about a quarter of its former size and, although still edematous and inflamed, it had regained its normal outline instead of presenting as an irregular proliferating mass. Slight bleeding occurred on touching it.

Since this paper was written a further opportunity of examining the patient has occurred, and on November 17, 1947, her cervix appeared normal, save for some slight increased vascularity around the os. Biopsy showed no evidence of malignancy; a smear and culture failed to demonstrate any pathogenic organisms and the Wassermann reaction and gonococcal fixation test were negative.

(See editorial note appended to preceding abstract.)

ICTERUS IN PREGNANCY: A CLINICO-PATHOLOGICAL STUDY INCLUDING LIVER-BIOPSY

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J. Obst. & Gynaec. Brit. Emp., **54**: 642–652, October, 1947

The etiology of liver damage in pregnancy as revealed by the symptoms of jaundice is still debatable. In pregnancy there may be repeated attacks of jaundice and this may appear early or late. The pregnant woman is more prone to acute liver atrophy than the nonpregnant. During the year 1932 (Peller, S., Der Geburtstod, 1936, Vienna) there was an incidence in England and Wales of 4.3 fatal cases of acute yellow atrophy in 100,000 pregnant women compared with 0.15 fatal cases in a similar number of nonpregnant.

The results of a clinico-pathological study are presented in this paper in the hope that they may elucidate the problem of icterus in pregnancy.

The cases are divided into 2 groups: (1) non-icteric (9 cases), and (2) *icteric* (12 cases). In all but one, liver biopsies were taken.

Liver-biopsies taken from 9 pregnant women (non-icteric) have not revealed gross, uniform, morphological changes from which one would be enabled to make the diagnosis of "liver of pregnancy." (Hofbauer, K., Zbl. Gynäk., **42**: 745, 1928.) In the past, German obstetricians have belabored this term unjustifiably. They have created such an entity based solely on functional findings which are notoriously unreliable. All that can be suggested is that there is a certain variability in cell-pattern about the liver in normal pregnancy, the significance of which cannot as yet be fully assessed. It may possibly be explained as being a morphological stigma of the strain of pregnancy. An extensive study of liver biopsies in nonpregnant and pregnant women (normal and toxemic) has been described by Ingerslev and Teilum (Acta. obstet. gynec. scand., **35**: 339, 1945) working in Copenhagen. Their findings are in agreement with ours in that the minor changes occurring in the liver during normal pregnancy are not specific enough to warrant the use of the term "liver of pregnancy" as though this were a histological entity.

Nine cases of this group showed histological changes common to the various types of hepatitis. The findings did not differ in any respect from those described by previous investigators. In the authors' material the diffuse acute form of hepatitis has prevailed. One case was typical of fulminating acute yellow atrophy. It was difficult to decide whether or not massive necrosis was superimposed upon hepatitis. The patient was seen 3 weeks before jaundice developed. When she was admitted jaundice had been present for only 3 days. Her nutritional state was poor and the serum protein low but not under 5 per cent.

On the basis of the pathological findings already discussed the clinical material (icteric and non-icteric cases) can be divided into 3 groups. The biochemical findings (Table III) support such a division:

(1) Non-jaundiced cases with more or less "hepatic strain."

(2) Jaundiced cases with histological findings similar to group (1).

(3) Jaundiced cases with a histological picture corresponding to hepatitis with a subgroup verging into acute liver atrophy.

This inversion of the albumin/globulin quotient is an important finding particularly as it can occur without visible morphological hepatic damage. It serves to differentiate the various types of jaundice in pregnancy. In infective hepatitis the serum proteins are more or less normal and especially the albumin/globulin quotient (Maclagen, N. F., Brit. Med. J., 2: 364, 1944; Teitelbaum, H., Curtis, H. C., and Goldhammer, G. M., Ann. int. Med., 22: 653, 1945). When in infective hepatitis there is inversion of this quotient it is a sign of the process becoming chronic and indicates scarring if such a liver were to be examined histologically.

The main question in infective hepatitis is whether or not the pregnancy is able to influence the course of the hepatitis. This disease has its specific etiology quite unrelated to pregnancy. Termination of pregnancy should be considered only if the hepatitis is of such severity that the life of the expectant mother is in serious danger. Statistics already quoted and the examples of Himsworth and Glynn (Lancet, 1: 457, 1944a) do show that pregnancy can influence infective hepatitis adversely. Ballot (Gaz. Hop. Paris, cited by Himsworth and Glynn (1944a) 1859) has described an epidemic in which 8 pregnant women were attacked by hepatitis and 7 of them died shortly before delivery. Hardie (Austral. med. Gaz., 9: 179 (1889–90) Cited by Himsworth and Glynn (1944a) reported a case of a young boy who had a mild attack of hepatitis. His pregnant sister later became jaundiced and died of acute yellow atrophy of the liver. Hayward (Austral. med. Gaz., 9: 17, 1889–90. Cited by Himsworth and Glynn, 1944a) has the bizarre record of a pregnant woman who died of acute yellow atrophy and 10 days later her husband developed infective hepatitis.

A common complication of acute infective hepatitis is the transition to a chronic form with development of cirrhosis. Massive necrosis is uncommon. But Himsworth and Glynn have indicated that the extra strain of pregnancy superimposed on infective hepatitis may contribute to a disastrous massive necrosis. They have underlined the nutritional element, deficiency of protein especially methionin, as a causal factor. German authors (Seyfarth, Dtsch. med. Wschr., 47: 1222, 1921; Strumpell, Dtsch. med. Wschr., 47: 1219, 1921) have described how in the first world war the incidence of acute liver atrophy was greatly increased and was related to the general malnutrition of their people. The one patient in the authors' series who succumbed to massive necrosis belonged to the lowest economic group. There was in 1936–37 in Istanbul (Liepmann, W., Proc. 3rd int. Congr. Obstet. Gynaec., Amsterdam, 2: 263, 1938) an epidemic of massive hepatic necrosis. The mortality was greatest among the poorest elements of the population.

When one recalls the large amount of nitrogen which a pregnant woman needs for the fetus and later for lactation one must agree with Himsworth and Glynn that nutrition may be a conditioning factor in the etiology of certain diseases. Thus the prognosis of infective hepatitis complicating pregnancy will depend on

the nutritional state.   The better this is the less the risk of an infective hepatitis progressing to acute atrophy.   The treatment of infective hepatitis in pregnancy should be directed towards the prevention of massive necrosis.   It is controversial whether evacuation of the uterus will influence the final changes in the liver. It may prevent massive necrosis.   Liepmann, in contrast to many obstetricians, was of the opinion that acute liver atrophy should not be included in the toxemias of pregnancy.   The authors are of the same opinion and suggest that termination of pregnancy should not be the invariable rule.   Such intervention rids the mother of the fetus but it does not treat the infective hepatitis.   Treatment should be guided by the nutritional state.   If in the early stages of jaundice malnutrition is obvious, then termination must be seriously considered.   On the other hand, if the level of nutrition is high then interruption of pregnancy is not such an urgent necessity.   The fate of the fetus is always doubtful in severe jaundice.

(See editorial note in February, 1948 issue of Survey, P. 16.—Ed.)

THIOURACIL IN THE TREATMENT OF HYPERTHYROIDISM COMPLICATING PREGNANCY: PRESENTATION OF TWO CASES

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Investigations in pregnant animals receiving thiouracil have suggested that the drug may have some effect on the fetus.   Goldsmith, Gordon et al (Am. J. Obst. & Gynec., 49: 197 (Feb.) 1945) reported inactivation of the thyroid gland in the offspring of rats fed thiourea in the diet.   Retarded growth and gland changes developed which were transient in nature, and which disappeared when the rats were placed on stock diet.

Davis and Fockes (Lancet, 1: 740, 1945) reported a case of sudden death in a young secundigravida, in the sixth month of pregnancy, under treatment with thiouracil for hyperthyroidism.   Examination of the fetal thyroid demonstrated changes in the gland similar to those observed in the thyroid of adults treated with thiourea.

Strouse and Drobkin (J. A. M. A., 131: 1494 (Aug.) 1946) reported one case of pregnancy complicated with hyperthyroidism and treated with thiouracil.   The mother made an excellent clinical response.   The baby was described "as not normal and having the appearance of a hypothyroid rather than hyperthyroid type."   The infant survived and apparently is developing normally.

Williams and Clute (J. A. M. A., 128: 65 (May) 1945) mentioned three cases

of pregnancy complicated with thyrotoxicosis in their series of 152 hyperthyroid patients. No particular mention of the course of these pregnancies was made. Two cases are presented in which thiouracil was used to treat hyperthyroidism complicating pregnancy. Both patients made a satisfactory clinical response to treatment with thiouracil, permitting completion of a normal pregnancy, and an uneventful delivery of normal infants. However, both patients showed manifestations of thiouracil toxicity in the immediate postpartum period which necessitated cessation of further drug therapy. Case 1 developed fever and conjunctivitis which were probably caused by thiouracil, and Case 2 developed leukopenia.

In both of our cases the infants appeared normal at birth. There was neither palpable thyroid enlargement nor evidence of disturbed thyroid state. The postnatal development has been entirely normal to date.

ACUTE APPENDICITIS IN PREGNANCY

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Clinical data on 23 cases of acute appendicitis in pregnancy are presented, much of which bears on several moot questions. Thus, it is the consensus that appendicitis is most frequently encountered during the first and second trimester of pregnancy. For instance, in 1921 DeLee is reported to have said that in 30 years of obstetric practice he had seen only 4 cases of appendicitis late in pregnancy. This was not true, however, in the present series, since 9 cases (39.1%) were observed in the first trimester, 6 (26.1%) in the second trimester and 8 (34.8%) in the third, that is, they found an almost equal division of their cases among the 3 trimesters. Among 9 patients with peritonitis, 4 or 44 per cent developed their attack in the last trimester.

Thirteen or 56.5 per cent of the patients gave a history of one or more previous attacks—for the most part in the course of the present pregnancy. This incidence of previous attacks is in close agreement with the figures previously reported by other authors.

The symptoms of appendicitis are the same in the gravid as in the non-gravid patient. As pregnancy advances, the pain is higher and more lateral. Nausea, vomiting, muscle spasm, rigidity, fever and leucocytosis are usually present in most cases, but the interpretation of these findings in the last trimester of pregnancy may be very difficult, because of the displacement of the appendix and cecum. The evaluation of symptoms referable to the gastrointestinal tract during pregnancy may prove rather confusing. This is especially true in cases of acute retrocecal appendicitis or in cases where the appendix is high in the region of the right kidney.

The authors believe that the differential diagnosis of acute appendicitis during the 3 trimesters should include the following:

1. During the first trimester:
   a. Ectopic pregnancy
   b. Salpingitis
   c. Early abortion
   d. Ovarian tumors
   e. Kidney or ureter stones.
2. During the second trimester: the above plus—
   a. Nephritis and pyelitis
   b. Gall bladder disease
   c. Intestinal obstruction
   d. Peptic ulcer
   e. Mesenteric lymphadenitis and thrombi
   f. Carbuncle of kidney
3. During the third trimester: the above plus—
   a. Premature labor
   b. Placenta previa
   c. Abruptio placentae
   d. Eclampsia

In regard to abortion and premature labor, the statistics in the literature vary from 2 to 26 per cent. The figure in the present series was 17.4 per cent. These complications are more common when the disease has spread beyond the appendix. When the authors' cases of immediate and late fetal loss were studied, the overall fetal mortality was found to be 42.9 per cent.

Maternal mortality is dependent on the duration of the infection and the period of gestation. After the 7th month, walling off of the infection is unlikely, and widespread involvement of the peritoneal cavity is a great possibility. There was 1 maternal death in the present series, a case in which the early picture suggested pyelitis; operation hence was not done; 36 hours after admission she manifested rapidly spreading peritonitis from which she succumbed.

The authors summarize their opinions on the treatment of acute appendicitis in pregnancy as follows:

1. *Prophylactic:* All pregnant patients should be closely watched for signs and symptoms of acute appendicitis, especially if there is a history of previous infection. When in doubt, it is best to operate, especially during the first 6 months. In women who have had attacks of appendicitis, appendectomy should be done, especially if the patient is contemplating marriage. It is our opinion that when the diagnosis of appendicitis has been made, appendectomy should be done regardless of the age of the patient, whether married or single, whether pregnant or not.

2. *During first 6 months:* Appendectomy is the procedure of choice. Maternal mortality is not increased and the diagnosis is not difficult.

3. *During last trimester:* Some believe that in the presence of acute appendicitis with perforation and generalized peritonitis, cesarean section should precede

PATHOLOGY OF PREGNANCY the appendectomy. Others believe that cesarean section should be done only in the very rare case. TeLinde and many others favor appendectomy only, regardless of the stage of pregnancy. The authors agree with TeLinde and would again add that they would rather take out an innocent appendix than miss an acute one.

They believe that during the prenatal period the obstetrician should watch carefully for signs and symptoms of appendicitis, especially in those patients giving a history of previous attacks. During the first and second trimester this should not be too difficult. During the last trimester the interpretation of signs and symptoms may be more difficult. When in doubt, and regardless of the period of gestation, they believe that operation is indicated.

When the appendix has been perforated more than 8 hours, and there is evidence of spreading peritonitis, it would seem that conservative management with antibiotics, penicillin and streptomycin is desirable. Following rupture of an acute appendix, local peritonitis follows. With continued leakage, this leads to generalized peritonitis with invasion of the peritoneum and lymphatics. The infection then becomes systemic and operation with or without drainage will offer the patient nothing. If such a patient is operated upon and drained, the drain soon becomes walled off with omentum and intestines. In generalized peritonitis it is impossible to drain the entire peritoneal cavity. George Crile, Jr. (Surg., Gynec. & Obst., 83: 150–162, August, 1946) has reported on the successful treatment of peritonitis with penicillin. He favors the use of 100,000 units of penicillin every 2 hours until the patient shows definite evidence of improvement. The dosage is then decreased to 50,000 units. Kennedy, McCadie and Arminski (Grace Hospital Bulletin, 25: 107, July, 1947) have recently reported a series of 80 cases of peritonitis treated with penicillin. They seem to favor a smaller dosage of penicillin (50,000 units), but state that better results are observed when these smaller dosages are combined with sulfonamides. If favorable results are obtained in the treatment of spreading peritonitis due to ruptured appendices with large doses of penicillin in the non-gravid patient, the authors see no reason why it should not be employed in the gravid patient. When the peritonitis, whether local or general, is not diagnosed until operation, the same dosages of penicillin and/or streptomycin should be employed. The liberal use of morphine seems rational. The use of progesterone is questionable.

HYPERPARATHYROIDISM AND PREGNANCY

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Hyperparathyroidism during pregnancy has been reported but rarely, only 7 cases having previously appeared in the literature. Three of the previously reported cases are reviewed. The first, a 29-year old woman, had had a history of hyperparathyroidism for 10 years and during her pregnancy she was thin and chronically ill. At the 4th month the pregnancy was interrupted. Autopsy of the fetus revealed normally developing osseous centers, bone structure and fetal parathyroids. The second case, a 32-year old Italian woman, para 12, had been bedridden for hyperparathyroidism for the last 3 of her pregnancies. The 11th infant was stillborn, but the 10th and 12th were normal in spite of extensive incapacitating skeletal changes in the mother. The third case involved the occurrence of tetany in a 5-months old infant whose mother was found to have hyperparathyroidism. It was stated that the mother's hyperparathyroidism had hampered the development of the fetal thyroid. The infant's hypocalcemia resisted the action of vitamin D and calcium by mouth. In most respects the baby described resembled other reported cases of tetany of the newborn.

The authors report a case of a 23-year old nullipara who was first seen in the fifth month of her pregnancy. Her past history revealed that she had been aware of a small lump in her neck for the past 4 years and at one time had taken iodine drops because of this lump. On physical examination there was a swelling in the anterior side of the neck above the left supersternal notch measuring about 2.5 x 2.5 cm. This mass moved with swallowing. There was also a hard, non-tender bulbous swelling at the point of her chin. Pelvic examination revealed changes compatible with gestation of 5 months' duration. Significant laboratory findings were: urine: trace of protein, but repeated examinations failed to reveal Bence-Jones protein; serum calcium 19 mg. per cent; serum inorganic phosphorus 3 mg. per cent; alkaline phosphatase 4 modified Bodansky units. The patient was placed on a calculated daily intake of 100 mg. of calcium and 500 mg. of phosphorus. Daily studies of urinary excretion of calcium revealed a negative calcium balance, ranging from −78 to −242 mg. X-rays of the chin showed a faintly calcified soft tissue tumor that arose from a discrete area of bone destruction in the mandible. Roentgenograms of other principal bones of the body demonstrated multiple destructive lesions associated with generalized decalcification of the skeleton. Roentgenograms of the kidney regions demonstrated collections of calcium granules in each kidney area. In the 6th month of her pregnancy the mass in the left side of her neck was surgically removed. The tumor weighed 13 grams. It was encapsulated, discrete and readily removed. A biopsy specimen was taken from the chin. Histological diagnosis was para-

thyroid adenoma. The biopsy of the skin tumor was interpreted as a rapidly growing giant cell tumor of bone. Calcium, phosphorus and phosphatase concentrations of her blood, determined at frequent intervals, revealed a rapid postoperative drop in the level of blood calcium. By the 3rd postoperative day the level had reached less than 11 mg. per cent and the serum phosphorus had risen to 3 mg. per cent. Ten weeks postoperatively x-rays revealed extensive recalcification of the skeleton. The patient completed her period of gestation without further mishap and at term gave birth to a normal female infant weighing 7 pounds 5¾ ounces. Roentgenograms of the baby's skeleton demonstrated no bony abnormalities. The serum calcium of the infant 3 days after birth was 10 mg. per cent. The postpartum period was uneventful. Directly prior to discharge the serum calcium was 11.7 mg. per cent, the serum phosphorus 3.3 mg. per cent.

In comment, the authors state that with cases such as this the principal concern of the physician should be with the mother since the report previously mentioned indicates that the fetus survives the mother's metabolic disturbances with relatively little if any change from the normal.

(As the authors state in the first sentence above, hyperparathyroidism is an extremely rare complication of pregnancy, their case being the 8th to be reported. These 8 cases are of interest not only because of their rarity but also because they bring out several points in regard to parathyroid behavior, both normal and abnormal, in gestation. Histological changes indicative of hyperactivity have been found in the parathyroid glands of normal pregnant women by several investigators (Seitz, L., Arch. f. Gynak.: *89*, 53, 1909); and it has been further shown that it is possible to extract from the blood of pregnant women a substance which behaves pharmacologically like parathyroid hormone,—a substance which is not to be found in the blood of non-pregnant persons (Hamilton, B. et al., J. Clin. Invest.: *15*, 327, 1936). This increase in parathyroid function occurs presumably in order to mobilize from bone trabeculae and other sites of recent calcium deposit an adequate amount of calcium for fetal needs.

If normal gestation is attended by more active parathyroid metabolism, it is understandable that any woman suffering from hyperparathyroidism might experience an exacerbation of signs and symptoms with the advent of pregnancy. This seems to hold true for most of the cases reported and in a few instances, indeed, the disease seems to have had its onset in association with pregnancy. Protocols of these cases and a thorough discussion of the problem may be found in Springarn and Geist's comprehensive article: J. A. M. A.: *113*, 2387, 1939.

The effect of maternal hyperparathyroidism on the fetus seems to be a moot question with the balance of evidence in favor of the belief that the parathyroid hormone does not pass through the placenta and that the fetus is not affected. This is in keeping with the findings in osteomalacia in which the fetus rarely (but sometimes) shows rickets.

If one of these cases should be encountered it would seem evident that the treatment lies in the field of parathyroid surgery, as exemplified by Pett and Clark's case, rather than in obstetrical intervention.—Ed.)

INTRA-ABDOMINAL HEMORRHAGE DURING PREGNANCY

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The loss of blood intra-abdominally during pregnancy is fortunately rare. Besides ectopic pregnancy, bleeding may occur from uterine rupture, rupture of a vessel on a uterine fibromyoma, ovarian abnormalities, trauma, rupture of varicose veins, genital and other malignancies during pregnancy. The bleeding is heralded by sudden abdominal pain followed by symptoms and signs of shock. There is little time for debate and speculation as the potential danger of severe sudden blood loss and resultant death make the diagnosis imperative and immediate treatment cardinal.

A case is presented in which a 31 year old patient, during the 5th month of her pregnancy, was seized with an acute intra-abdominal hemorrhage. At laparotomy there was an irregular longitudinal break in a varicose vein at the base of the posterior right broad ligament. The measured blood loss was 2200 cc. The fragmented vein was clamped and sutured and the bleeding was thus controlled. The following day the patient aborted. The postoperative course was otherwise uneventful.

Harding and Concanon reviewed the literature and found 12 such cases. Seven of the cases were discovered at autopsy and there were 6 survivors including their case. In regard to the surgical management of this type of hemorrhage the author favors simple ligation of the bleeding vessel as the easiest and quickest possible solution for these shocked women. He stresses the prompt and complete replacement of the blood loss by blood transfusion.

(Anyone interested in further study of this rare and dramatic complication of gestation should consult J. R. Miller's scholarly and comprehensive review of the literature published in the Am. J. Obstet., & Gynec.: *16*, 103, 1928. The article mentioned in the above abstract by Harding and Concanon (*J. Obst., & Gyn., Brit. Emp.: 50*, 208, 1943) reviews the cases reported since Miller's publication.

Cases such as that abstracted above in which a varicose vein ruptures directly into the peritoneal cavity are to be differentiated from a rather larger group in which broad ligament hematomata rupture into the abdominal cavity and also from intraperitoneal hemorrhage from myomata. In Harding and Concanon's case, rupture of a vein on the posterior surface of the uterus was brought about by coitus, some 3 to 4 pints of blood being found in the peritoneal cavity. In the one case I have seen of this complication (intra-abdominal bleeding due to rupture of a varicose vein on the anterior surface of a full term uterus), the clinical picture resembled that of premature separation of the placenta: acute abdominal pain, increasing tenderness of the abdomen and signs of internal hemorrhage in the absence of external bleeding. These cases are so rare, of course, that they belong to the curiosities of obstetrics.—Ed.)

PATHOLOGY OF LABOR AND PUERPERIUM

ACUTE INVERSION OF THE UTERUS TREATED BY HUNTINGTON'S OPERATION

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Huntington (Boston med. surg. J., **184**: 376, 1921) described an abdominal operation which he had used in 1 case in the acute phase when vaginal replacement had failed and the patient was still bleeding. The hemorrhage and shock were treated by blood transfusion before and during operation and she recovered. Its successful use was recorded in 7 more cases by Huntington, Irving and Kellogg (Am. J. Obst. & Gynec., **15**: 34, 1928) and Irving and Kellogg (Am. J. Obst. & Gynec., **22**: 440, 1931). In 4 of these, vaginal replacement had been tried and the vagina packed for hemorrhage before abdominal operation. Two further successful cases have been recorded by Dawson (N. Z. med. J., **42**: 15, 1943) and in 1 of these 2 attempts at vaginal replacement had been made at 24-hour intervals prior to Huntington's operation. In only 1 case so far recorded has a patient died following Huntington's operation for replacement of the uterus (Harer and Sharkey, J. A. M. A., **114**: 2289, 1940) but details are not given as to whether she had transfusion-therapy. Irving (Curtis' Textbook of Obstetrics and Gynaecology, 2nd ed., Vol. III, Saunders, Philadelphia, p. 650) recommended that the operation should be used without even attempting vaginal replacement. This was because the operation does not increase shock or hemorrhage, which vaginal manipulations tend to do, and it is technically simple, taking only 15 minutes to perform.

The technique consists of an abdominal incision about 3 inches long to expose the inversion cup. The operator and his assistant, using Allis' forceps, grasp the posterior uterine wall on either side, about ¾ inch below and inside the inversion cup and draw it up. A further 2 pairs of Allis' forceps then grasp the uterus at a lower level and elevate it; the first pair is then removed and re-applied below the second and so on until the fundus is up and reinversion is complete. Any small abrasions in the uterine wall caused by the forceps are sutured with catgut. The abdomen is then closed. Irving and Kellogg described a modification in technique using Allis' forceps at one uterine cornu only and they found the reposition successful in the 2 cases so treated.

A case is recorded of acute inversion treated by Huntington's operation after attempts at vaginal replacement had failed. The ease of the operation was confirmed and the fact that it takes only 15 minutes to do.

The authors' object in recording this case is to recommend the extended use of

Huntington's operation in cases where vaginal replacement of the inverted uterus fails, bleeding continues and the patient remains shocked. The improvement in general condition after abdominal replacement of the uterus is dramatic, and bleeding stops immediately.

(For further endorsement of this procedure—at least, speculative—see editorial note in December 1947 issue of Survey, pp. 791–793.)

THE INTRAUTERINE PACK IN THE MANAGEMENT OF POSTPARTUM HEMORRHAGE

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While there has been a striking decrease in maternal death rate from puerperal sepsis and toxemias, mortality from obstetric hemorrhage, the largest proportion postpartum hemorrhage, has changed little. Analysis indicates that although deaths from postpartum hemorrhage are not entirely preventable, they are almost preventable under ideal conditions, which include adequate prenatal care, conservative management of labor and its 3rd stage, hemostasis, and the replacement of lost blood volume.

The employment of the intrauterine pack for postpartum hemorrhage is a controversial subject. Some writers maintain that its use is unphysiologic, that it holds open the uterine sinuses, allowing continued loss of blood, and that the uterus then distends and a concealed hemorrhage is developed. They prefer oxytocics and other methods including bimanual compression. The use of a hot intrauterine douche before resort to packing has been advised by certain British authors. Other obstetricians have said that tamponade should be used as soon as it becomes evident that hemorrhage is not being controlled by the usual available methods, that the pack acts to control bleeding by actual tamponade and by serving as a foreign body to stimulate uterine contraction. The type of pack used varies.

During most of the present study 1.0 cc. of alpha-hypophamine (pitocin) has usually been given intramuscularly during delivery of the head and shoulders of the baby. When evidence of separation of the placenta is present, and the placenta has not been expelled spontaneously, or if copious bleeding occurs, the placenta is delivered by simple expression. If the placenta is retained without signs of separation for more than 20 minutes, or if bleeding persists, the Credé maneuver is attempted and if necessary is repeated at about 10-minute intervals for an hour or so postpartum. Sufficient anesthetization to relax the uterus

sometimes helps. If the placenta has not been delivered within an hour, or if bleeding requires earlier interference, manual removal is done. After delivery of the placenta, an atonic uterus or persistent bleeding indicates the need for vigorous massage of the fundus and usually for intramuscular or preferably intravenous administration of an ergot preparation.

If excessive bleeding continues, the uterus is packed firmly with sterile gauze. Packing is most imperative if the uterus continues to relax. "Two fingers are inserted in the uterus, with the palm of the hand anterior. The gauze is carried along the fingers with a blunt-nose packing forceps or placental forceps or, in some instances, with the first and second fingers of the other hand. Washed iodoform gauze 2 inches (5 cm.) wide in 5 yard (4.6 cm.) lengths is employed, and several lengths are tied together when more packing is necessary to fill the uterus completely. In cases of severe bleeding from an atonic uterus, the vagina also is packed tightly. When the delivery has been complicated by placenta previa, uterine and vaginal packs usually are placed as a precautionary measure, even though bleeding is not pronounced." The pack remains in place 4–30 hours.

This procedure has been carried out without undue delay where oxytocics and massage did not readily control bleeding in 267 (2.3 per cent) among about 12,000 deliveries at the Mayo Clinic from 1918 through 1945. The most frequent single indication for packing was persistent uterine hemorrhage after the 3rd stage of labor (106 cases). The average blood loss in these cases was 690 cc. for primiparas and 620.7 cc. for multiparas. Other packs were done for hemorrhage persisting after manual removal of the placenta. Tamponade was used also as a prophylactic measure because of persistent uterine atony after manual removal of the placenta or after cessation of bleeding in 115 of the 267 cases. It is felt that in these cases tamponade is a valuable prophylactic measure in the event that firm contraction is not induced promptly by other means.

Six of the patients continued to bleed through the pack. In 3 the bleeding was controlled by repacking. However, the remaining 3 could not be controlled by oxytocics, massage, or repacking, and abdominal hysterectomy was therefore done. In 1 of these there was rupture of the uterus—possibly caused when the placenta was removed, or by violence of contractions during her precipitate labor, or by packing of the uterus.

The morbidity rate for the patients in whom uterine tamponade was done was ·10.9 per cent, as compared with the morbidity rate of 13.1 per cent among patients who were anemic as a result of postpartum hemorrhage and whose uteruses were not packed. The 1 death occurred (before the advent of chemotherapy) in a multipara in whom rupture of the amniotic sac occurred 48 hours before onset of labor; several vaginal examinations were done before she was brought to the hospital, and the placenta was eventually removed and the uterus packed after delivery of triplets; there was postpartum febrile morbidity, and hemolytic streptococci were found in the uterus.

In more than 30 years, only 1 patient has shown sensitivity to iodine in the iodoform pack—a slight generalized erythema.

It is felt that the intrauterine iodoform pack as a method of hemostasis gives excellent results when carried out aseptically before the loss of blood becomes severe.

Discussion about the use of packing was both pro and con, and may be summarized somewhat as follows:

On the one hand, uterine tamponade carefully and efficiently performed without delay is often a life-saving measure. It is better in some environments to prevent loss of blood by packing the uterus, than to attempt to replace blood loss where transfusion is not immediately available. For the present, while a uterine pack should be rarely necessary, it should always be available.

On the other hand, uterine tamponade directly circumvents the efforts otherwise made to empty completely the uterine cavity, reduce that cavity to the smallest size possible and the bulk of the myometrium to the smallest mass possible. It is unnecessary in the less severe cases and futile in the more severe ones. It may actually militate against the patient by loss of time in resorting to more definitive surgical measures, by obscuring accurate diagnosis, and by hiding continuing significant hemorrhage.

The hazard of overpacking was mentioned. The possibility of new agents and chemicals for packing was suggested. The place of oxytocics in reducing the necessity for tamponade was commented upon, although 1 discussant questioned whether oxytocics are safe for the instruction of medical students and interns. In Cleveland, pituitrin is given directly upon the birth of the child, and an ergot preparation immediately upon the separation of the placenta. In about 100,000 cases there have been no instances of retention attributable to pituitrin. Packing for postpartum hemorrhage is very rarely used—not for years by some there. In addition to the routine administration, a hand should be kept continuously on the fundus during the 3rd stage, and if relaxation occurs the oxytocics should be repeated.

The discussants agreed upon the great importance of the management of the 3rd stage of labor, and the need for better prenatal care. 3 tables.

(As the authors point out, packing of the uterus for postpartum hemorrhage is a controversial subject. The main purpose of the above paper is to endorse the procedure; and coming from such an experienced and sane clinician as Mussey, it cannot be taken lightly. Moreover, the record reported is excellent: 12,000 deliveries with not a single maternal death as the direct result of postpartum hemorrhage, the uterus having been packed promptly for hemorrhage in 2.3 per cent of the cases, or in 267.

Offhand, of course, the above record speaks well for uterine packing. However, as a matter of interest, I have just looked over our annual reports for the past 5 years, which happen to yield an almost identical number of deliveries as reported in the above article, that is, 11,886. In this entire series we packed the uterus only *twice*. Yet no woman died of postpartum hemorrhage and only one hysterectomy had to be done for this cause,—this in a patient who bled through her pack. So you can take your choice,—after a little thinking.—Ed.)

PRIMARY FACE PRESENTATION

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Hyperextension of the head before the onset of labor is very rare; it is more likely to occur after labor has set in, resulting in a brow or face presentation.

A case is presented of a 25-year-old primigravida, seen in consultation 5 weeks after the expected date of delivery. X-ray examination at the anticipated time of delivery showed a face presentation at the inlet. The prenatal course had been uneventful. According to the measurements there was a slight cephalo-pelvic disproportion; spontaneous delivery might ensue should the head come through in its shortest diameter, and a test of labor was advised.

At the time of consultation patient had no complaints and findings on examination were essentially negative. Another x-ray study of the pelvis showed a single fetus with the face over the right side of the pelvic inlet and the fetal spine on the maternal left side. According to measurements, with a presentation of a more ordinary variety, delivery from below could be accomplished. However, in this presentation, such delivery might be dangerous to the fetus. Considering the fact that the patient was definitely postmature, with some cephalo-pelvic disproportion and extreme hyperextension of the fetal head, further delay seemed inadvisable. A low flap cesarean section was performed the next day under fractional spinal anesthesia. A livid baby boy, 8 pounds 14 ounces, was delivered. The amniotic fluid and the skin were meconium stained, a sign of fetal embarrassment. The head remained hyperextended for some time and there was an indentation between the scapulae where the occiput was pressing against the spine. Only after suction of the trachea and administration of oxygen did the baby begin to breathe; respirations were irregular and the cry feeble. In spite of incubator and supportive treatment, the infant died in about 12 hours. Autopsy showed atelectasis of both lungs and dilatation of the right ventricle. The mother's recovery was uneventful.

Posner and Buch, studying face and persistent brow presentation, showed that there was a higher incidence of maternal and fetal morbidity and mortality in cases of extension of the head, and advocated greater consideration for cesarean section (Surg., Gynec. & Obst., 77: 618, 1943). In cases such as this, where the condition is recognized early, cesarean section as soon as viability is certain would lessen the danger to the fetus from its long, abnormal position and might avoid fetal deaths. 3 figures.

(Prior to the days of X-ray pelvimetry, it was generally believed that face presentations never develop before the onset of labor except in rare instances of fetal goiter and the like. Nowadays, when X-ray studies are frequently made in the latter weeks of pregnancy, a face presentation will turn up occasionally and at least 3 such cases, that is, face presentations prior to the onset of labor, have come to my attention in the last 10 years.

No sensible obstetrician would quibble about Brody's decision to perform cesarean section in this case in which a large baby presented by the face in a pelvis which was slightly contracted. It is also true that face and brow presentations carry increased fetal mortality rates and that, for a number of reasons, this group of cases will call for abdominal delivery more often than occiput presentations. Nevertheless, I am not so sure that cesarean section simply because of the distorted position of the fetus and the possibility of resultant injury to the upper respiratory tract, is warranted. This would mean routine cesarean section in any face presentation near term which was discovered before the onset of labor. It may have been due to good luck, but the outcome to the infant in the 3 face cases of this sort I have followed—all delivered vaginally—was satisfactory. The general idea of pressure effects on the fetus in utero, however, is a valid one and is occasionally exemplified also in neglected transverse positions when one lung may be completely compressed and atelectatic while the other one is normal.—Ed.)

PUERPERAL SUBPERITONEAL HEMATOMA—CASE REPORT

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The vulvar and perineal varieties of hematoma are not uncommon and usually not serious. Less frequent is vaginal hematoma in which the blood collects in the connective tissue of the vaginal wall. This variety also usually is not of serious prognostic importance although if it occurs during delivery it may cause obstruction in the birth canal.

Still less frequent is the subperitoneal type of hematoma in which the blood lies beneath the peritoneum but above the pelvic floor. According to Williams (Trans. Am. Gynec. Soc., 1904) it usually follows incomplete rupture of the uterus or deep cervical tears but in a small number of cases, as in the case here reported, the hemorrhage apparently results from rupture of the vessels within the broad ligament.

The patient, a 39 year old married para 8 gravida 12 abortus 3, was admitted to the obstetrical service of Grace-New Haven Community Hospital on October 31, 1947, in active labor and with a history of ruptured membranes. The present pregnancy had been essentially uneventful, but the patient had noted increased vulvar varicosities and some venous varicosities of the right leg during the 3rd trimester. The expected date of confinement was October 17, 1947.

After a rapidly progressing 3 hour labor the patient was delivered spontaneously of a 3815 gram baby boy, a few whiffs of nitrous oxide being utilized for anesthesia during contractions. The 3rd stage of labor was completed in 30 minutes, the placenta being expressed from the vagina. Blood loss was estimated at 50 cc., blood pressure at the end of labor was 105/75. The placenta on inspection appeared to be intact. The patient was given 1 cc. of pitocin and 1 cc. of ergotrate after the delivery of the placenta.

An hour after delivery the patient was returned to the obstetrical floor at which time she noted the gradual onset of right lower quadrant pain which rapidly became quite unbearable. Three hours after delivery the fundus was found to be 6 cm. above the umbilicus and resting beneath the costal margin on the left. The uterus was firm; lochia was moderately heavy with several clots of blood being expressed. Along the lower right margin of the uterus an extremely tender indefinite mass extending to about 4 cm. below the umbilicus was made out. There was no rebound tenderness or spasm. Blood pressure at this time was 118/76 with pulse 87, somewhat weak. The diagnosis of hemorrhage into the right broad ligament was made at this time.

During the next 12 hours the right lower quadrant pain persisted, relieved only by morphine. Vital signs remained stable. However, blood studies showed a drop from 14 grams hemoglobin on admission to 11.5 grams. An x-ray of the lower abdomen at this time showed the presence of a large mass, extending from the pelvis to the level of the second lumbar vertebra on the left interpreted as being the uterus, and a suggestion of another mass on the right of the abdomen extending down into the pelvis which mass was thought to represent the hemorrhage into the broad ligament. Inasmuch as the patient's blood pressure stabilized at about 100/70 with pulse of 88, it was decided that the patient should be watched carefully and laparotomy carried out if there were signs of further hemorrhage.

During the afternoon of the first postpartum day the patient noted the extension of pain to the right flank. At this time the mass in the right lower quadrant was well defined by palpation extending to the lower margin of the umbilicus. It remained very tender, though less so than on the day of delivery. There was also marked tenderness in the right costovertebral angle, though no fulness or mass could be demonstrated here. The uterine fundus remained high on the left and was firmly contracted. The lochia was moderate with only occasional small clots being passed. The distribution of pain and a drop in red count to 3.1 million with 10 grams of hemoglobin suggested the continuance of hemorrhage retroperitoneally along the ureter into the right subrenal area. During the first postpartum day she was kept fairly comfortable with codeine and aspirin, morphine being required only twice when the other medications seemed ineffective. Toward the end of the first postpartum day the blood pressure had fallen to 80/55 with pulse between 80 and 90 and red count of 2.47 million with 8 grams of hemoglobin.

The 2nd postpartum day she felt more comfortable with only moderate right lower quadrant and flank pain which was fairly well controlled with codeine and aspirin. She was given 500 cc. of whole blood which was repeated the following day.

On the 5th postpartum day the patient was seized suddenly with a violent shaking chill with rapid temperature rise to 105.6°. She became dyspneic and apprehensive. Physical examination at this time revealed that the chest was clear. The uterus was firmly contracted and in the left lower quadrant. There was marked right costovertebral tenderness on the right and slight calf tenderness

on the right. Homan's sign was negative. Blood culture taken during the shaking chill subsequently showed no growth. The patient was given sulfadiazine in full doses to supplement the penicillin. The next day (postpartum day 6) her temperature was 102°.

During the 6th postpartum day the patient noted the gradual onset of chest pain which was most prominent in the right lower chest, though she had some fleeting pain on the left side also. The pain here was definitely increased by deep inspiration. Examination of the chest revealed little except for dulness to percussion and diminution of breath sounds in the right base. X-ray of the chest revealed no abnormalities other than an elevated diaphragm on the right. Also, the roentgenologist remarked that "the whole right subdiaphragmatic area is of greater density than normally observed." At this time temperature was 101°. Red count was 2.16 million with 9.15 grams of hemoglobin. She was given another 500 cc. transfusion of compatible whole blood.

The patient's temperature flattened out after the 13th postpartum day. Her lochia remained moderate rubra until the 14th day and with continued improvement she was gradually mobilized and was discharged home on the 21st postpartum day on a regime of semi-bed rest.

The patient was seen in the clinic 2 weeks after discharge at which time she had no complaints. On examination of the pelvis there was no trace of any mass and the uterus was fairly well involuted. She was seen again 3 months postpartum at which time she claimed to be in excellent general health. At this time she complained of occasional "twinges" of pain in the right lower quadrant and kidney region on the right. She had not had a menstrual period since delivery which led her to inquire as to whether she were not again pregnant. Pelvic examination at this time was essentially negative, although there was a very slight sensitiveness in the right parametrial region. X-ray of the lower abdomen at this time was read as indeterminate.

THE NEWBORN

PARENTERAL PLASMA AS AN ADJUVANT TO PREMATURE NEWBORN MANAGEMENT

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This experiment was undertaken in an attempt to meet 2 problems in the management and development of the premature newborn. First, the normal premature newborn is recognized as having a hypoproteinemia. Second, the nourishment offered the premature newborn, either in the form of breast milk or a formula of cow's milk, no matter how rapidly increased and still tolerated, does not supply the amount of protein necessary to correct the hypoproteinemia and to support growth.

It was thought that protein by hypodermoclysis might supply this much needed food and at the same time eliminate an overburden on the gastrointestinal tract. By so supplying the premature newborn with this added protein, it was hoped that the hospital stay of the premature infant would be lessened by directly improving its nutrition, and indirectly reducing the need of blood transfusions by aborting the so-called "physiological anemia of the newborn."

It was found from experience that a 50 per cent plasma solution in 2½ per cent glucose and physiological salt solution was absorbed best, and that after repeated clyses an interval of 72 hours was the optimum for complete absorption. Therefore, the hypodermoclyses were started on the second or third day of life and given every third day until the baby weighed above 2500 grams. The plasma used was obtained from Red Cross surplus of lyophilized human plasma. In use, the plasma is dissolved in the sterile water supplied in the carton, and this solution is then diluted with an equal volume of 2½ per cent glucose in physiological saline. A transfusion drip filter is then inserted midway in the tubing from the flask to a Becton Dickinson luer-lok control syringe equipped with a 3-way ball valve stopcock. This in turn receives a 3-inch 20 gauge spinal needle.

The scapular and interscapular area is thoroughly cleansed with 70 per cent alcohol, and the needle inserted subcutaneously pointing caudad. The entire needle is then introduced, keeping it in the loose subcutaneous areolar tissue, usually to an area just superior to one of the iliac crests. One-half of the quantity to be given is then deposited, starting at this level and withdrawing the needle as injection continues. Before the needle point leaves the skin, it is then readily directed to the other side, its entire length introduced and the procedure of deposition repeated. Occasionally, the needle will have to be reinserted on the opposite side to facilitate the deposition of all the solution. With the total amount given, the needle is withdrawn and pressure is maintained over the puncture site until

it is sealed.   This usually takes a few minutes.   Occasionally, minimal bleeding is encountered.   The author has never found it a contraindication for further clysis.   In further protecting the site of puncture, an alcohol gauze is left over it for 12 hours.

The amount of 50 per cent plasma used is roughly 10 cc. of solution per pound body weight at the time of injection.   The nursery is divided into 3 convenient weight groups: 1000–1500; 1500–2000; and 2000–2500 grams.   Respectively, each group receives 30, 40, and 50 cc. (roughly 1.0, 1.4, and 1.7 g. of protein).

A total of 1960 clyses were given to the 500 babies in the experimental group, and only 4, or 0.07 per cent, infected pockets of plasma were observed.   All infected pockets were treated with aspiration and then instillation of penicillin solution.   Hemolytic Staphylococcus aureus was the predominant cause of infection.   The abscesses cleared dramatically, usually after only one such treatment. There were no fatalities in any way referable to the plasma clyses.

SUMMARY

1. Parenteral plasma by hypodermoclysis is in no way injurious to the premature newborn.   It is tolerated well and absorbed completely.   No febrile reaction is observed except in the presence of secondary infection.

2. The general condition of all prematures receiving this treatment was noted to be improved over those not receiving it.

3. It is possible that parenteral plasma as administered reduced the severity of anemia in the premature, thereby diminishing the number of blood transfusions given to those babies requiring them.

4. It has been observed that a premature who is vigorous enough to survive the first 3 days of neonatal life has passed the critical period, and has a good chance of surviving at least the neonatal period.

5. In the babies whose birth weight was between 2000 and 2500 grams, parenteral plasma had significant value.   It definitely reduced the persistence of premature status by 3.3 days.   Although no such claim can be offered for the other 2 groups, it is felt that there was appreciable benefit as to their general condition.

(It is a pleasure to welcome this new journal to our midst.   As might be expected from its source, the first 2 issues are full of sound, practical information.—Ed.)

POSTMORTEM OBSERVATIONS IN TWENTY-TWO PREMATURE INFANTS

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Better cooperation, by clinicians in obtaining permission for postmortem examinations and by pathologists in performing adequate examinations, is needed to remove the misconception that prematurity alone is an adequate cause of death in premature infants dying in the neonatal period, and to increase the basis for clinical diagnosis.

Consecutive autopsy records of 22 premature infants dying during the neonatal period on Tulane Service of the Charity Hospital of Louisiana are studied here; all infants were born alive, weighed more than 499 and less than 2500 grams, and died between 5 minutes and 25 days after birth. Complete postmortem examinations were done on all. Bacteriologic studies were inadequate since most of the bodies were unclaimed and by law the autopsies could not be done for 48 hours.

Five of the infants were previable (weight 500–999 grams). In 2 of these the cause of death was bronchopneumonia and in 2 intracranial hemorrhage; no adequate cause could be demonstrated in the 5th.

Of the entire 22, bronchopneumonia was the immediate cause of death in 6 cases, in infants dying from 17 minutes to 25 days after birth, and was an incidental factor in 4 others. It was more severe and probably represented a postnatal infection in the infants who lived over 48 hours. Three of the 4 dying during the first 24 hours showed microscopic evidence of aspiration of amniotic sac contents. In 2 the inflammation was slight and asphyxiation may well have been more important. Premature infants appear to be especially susceptible to respiratory tract infections.

Congenital syphilis accounted for 5 deaths, from 1½ hours to 34 hours after birth. The osseous changes were constant; other evidences found of congenital syphilis were hepatomegaly and splenomegaly, syphilitic pancreatitis, and extensive fibrosis of the hypophysis. While not an important cause of abortion, syphilis is an important cause of premature delivery.

Asphyxia accounted for 4 deaths, all within 24 hours. While small amounts of amniotic sac contents are often found in the lungs, a large amount is indicative of fetal asphyxia. Such matter may be identified by a pink staining coagulum applied to respiratory surfaces, the so-called asphyxial membrane, and by presence of cornified epithelial cells entrapped in the membrane or free in the air spaces. In these infants there were keratinized epithelial cells in the air spaces and a pink amorphous membrane lining many of the bronchioles. Wilson and Farber believe actual bronchial obstruction due to aspiration of amniotic contents

to be more frequent in full-term than in premature infants, since production of vernix and cornification of the skin take place largely in the last months of pregnancy.

Moderate to slight aspiration of amniotic sac contents was found in 8 others in which asphyxia may have been a contributing cause of death; 2 of these showed a few small foci of subependymal encephalomalacia in the white matter by the lateral ventricles, possibly from asphyxia or from birth injury, and similar to those reported in brains of mentally deficient children.

Intracranial hemorrhage was responsible for 4 deaths, in 5 minutes to 31 hours: 1 extensive subarachnoid hemorrhage and scattered petechiae in the brain; 2 subarachnoid, intraventricular and small intracerebral hemorrhages; and 1 intraventricular hemorrhage and petechiae in the brain. There was no associated tear in the falx or tentorium. In such cases there is great difficulty in distinguishing between traumatic and asphyxial intracranial hemorrhage.

Thrombosis of the dural sinuses accounted for 2 deaths, after 14 and 18 days, with no local inflammatory basis evident. Bailey and Hass and Byers and Hass have emphasized acute nutritional disturbances in the pathogenesis of dural sinus thrombosis in early life.

Prematurity of course favors the occurrence of such lesions as intraventricular hemorrhage. The full-term infant may survive trauma and infection which might kill the premature, and has a pulmonary reserve which the premature lacks. However, the findings indicate that prematurity uncomplicated by other disorders is seldom the sole cause of death. 1 table.

INADEQUATE MATERNAL NUTRITION AND HYDROCEPHALUS IN INFANT RATS

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Richardson and Hogan observed hydrocephalus in infants rats as the result of feeding an inadequate diet to the mother. In order to check the findings through an unrelated colony of rats, 38 females from the suitable colony at the Texas Station were given diet A, essentially the same in composition as that used by Richardson and Hogan: casein (acid washed), 25 gm.; Cerelose, 57 gm.; wood pulp, 3 gm.; salts, 5 gm.; lard, 10 gm.; choline chloride, 0.1 g.; inositol, 0.01 g.; p-amino-benzoic acid, 0.05 g.; vitamin A, 3000 I.U.; vitamin D, 425 I.U.; α-tocopherol, 2.5 mg.; Menadione, 2.5 mg.; thiamine chloride, 1.0 mg.; riboflavin, 1.0 mg.; pyridoxine hydrochloride, 1.0 mg.; calcium pantothenate, 4.0 mg.; niacin, 5.0 mg.; and biotin, 0.02 mg.

Some of the experimental females were from mothers which received a stock

diet, others from mothers which received a synthetic diet. In every case they received diet A from 28 days of age until it was evident that no additional young would be produced.

A total of 10 young have developed typical hydrocephalus—an incidence of 1.5 per cent, approximately the same as that in the earlier report. None has occurred in the offspring of females which received a stock diet of natural feedstuffs. The hydrocephalus in 5 of these 10 young was identified at birth, again when they were 10 days old by observing the transmission of light through the brain cavity, and finally by autopsy. It was not identified in the other 5 until they were about 10 days old. Twelve additional young appeared to be hydrocephalic at birth, but none of these survived more than 2 days, and the early identifications have not been entirely reliable.

Earlier observation suggested that a small amount of yeast in the diet would furnish very little, if any, of the factor preventing hydrocephalus and would supply sufficient pteroylglutamic acid for normal reproduction.

Intestinal synthesis of some unrecognized factor might decrease the incidence of hydrocephalus. The addition of a sulfonamide to the diet would decrease this intestinal synthesis and thus increase the incidence of the abnormality. To test this possibility, 12 females were given diet B, the same as diet A with 2 per cent of dried yeast and 1 per cent of sulfasuxidine substituted for equal amounts of Cerelose. Of 92 young produced so far, none has been hydrocephalic. While too insufficient to be conclusive, these data indicate that the addition of sulfasuxidine to the diet does not increase the incidence of the abnormality under these conditions.

MENTAL DEFICIENCY OF PRENATAL ORIGIN: A CHALLENGE TO PREVENTIVE MEDICINE

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Benda's data show that 2–4 per cent of the population have some degree of subnormal mental development, and that causes of idiocy and imbecility are 40–50 per cent antenatal; 30–40 per cent of the severe cases appear in families which could expect normal offspring. The distribution of types in the 200 autopsies he reviewed included 50 cases of mongolism, 19 microcephalics, 13 hydrocephalics, 5 cases of congenital syphilis, 2 Kernicterus, 20 familial morons and high-grade imbeciles and 15 endogenous idiots and low-grade imbeciles.

Many hereditary traits produce mental deficiency, with or without gross malformations. Successful prevention must be based on knowledge of the genetics of the trait. A nationwide effort may be necessary to obtain statistically signifi-

cant information for a program of eugenics. Snyder (Amer. Naturalist, 76: 129, 1942) has reviewed the factors to be considered in such analysis.

Congenital syphilis is one of the fetal infections leading to defects of mental development, eyesight and hearing. About 5 per cent of those with congenital syphilis develop neurosyphilis, and one study of mental defectives indicated congenital syphilis as the cause in 1.7 per cent. Effective antisyphilitic treatment of the mother has reduced the incidence. Moore has written of the problems involved (The Modern Treatment of Syphilis, London, Bailliere, Tindall & Cox, 1941).

Transmission of toxoplasma from the mother to the fetus may produce severe changes including encephalitis, hydrocephalus, and chorioretinitis. Further research must attempt to detect carriers and to prevent or combat infection.

Many workers have described malformations and abnormalities, including mental deficiency, deaf-mutism, and blindness, in children whose mothers contracted certain virus diseases, usually rubella, during the early months of pregnancy. A high incidence of maldevelopment is suggested. Preventive measures should aim at control of rubella during the child-bearing age. It is not known whether the fetus is infected with rubella or suffers from the changes in the maternal organism. In many cases microcephaly has been found, and recently mongolism. Additional autopsy findings are needed.

Endemic cretinism follows deficiency of thyroid hormone or iodine in the maternal environment. Hurxthal and Musulin (Am. J. Med., 1: 56, 1946) have shown that the problem of origin is far from solved and that both environmental and intrinsic factors must be considered. Preventive use of iodine has apparently reduced the incidence in some areas. The pathological changes in the brain are not well known.

Ingalls (Am. J. Dis. Child., 73: 279, 1947) concludes that no existing theory satisfactorily explains all known features of mongolism. Various writers have suggested a maternal pituitary deficiency, an abnormal uterine environment, or some genetic factor. Inconspicuous pathological changes have been described in the brain, and a peculiar kind of cataract and other malformations have been found.

Fetal oxygen deficiency as a cause of brain damage and subsequent mental defect occurs most commonly during labor but may happen earlier. In human cases it is difficult to decide whether brain damage is cause or sequel of anoxia, but there are good indications that in some cases the cerebral changes are produced by anoxia. Proper prenatal and obstetric care should reduce the incidence.

A recent statistical study suggests that milder forms of erythroblastosis fetalis may account for many cases of undifferentiated mental deficiency. The pathologic mechanism is not clear, and the recent suggestion that agglutination thrombi in cerebral vessels are the cause of brain damage needs study.

The possibility of microcephaly, hydrocephalus, microphthalmia and other defects from irradiation of the fetus is well recognized. It is suggested that therapeutic doses of x-rays or radium to the pelvic region of a woman of child-

bearing age be preceded by a diagnostic curettage to avoid irradiating a possible fetus. Diagnostic doses for roentgenograms are not known to be harmful; fluoroscopy should be done most cautiously. This problem is different from the question of the influence of radiations on the genotype, producing mutations which determine hereditary malformations in the offspring; occurrence of the latter has not been established in man, but protection of the gonads from irradiation is advised.

Mechanical injury to the brain or meninges should be rare under proper obstetrical care. Other causes of mental deficiency still need to be recognized. Nearly any field in medicine can contribute toward the prevention of mental deficiency, and the cost of the most extravagant research program may well be less than the community savings from a reduced number of inmates in institutions. 1 table.

ERYTHROBLASTOSIS FETALIS IN NEGROID INFANTS

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The incidence of erythroblastosis among Caucasoids is reported from 1:400 to 1:150 births. No reports have been noted, however, concerning appearance of the disease in Negroid infants. Three such cases having unusual features are presented here.

The 1st child, apparently normal, born following an uncomplicated pregnancy and labor, with the only abnormality at delivery a yellow discoloration of the vernix and amniotic fluid, developed moderate icterus of the skin and sclerae on the 2nd day of life. There was no enlargement of liver or spleen. Next day jaundice became more intense and the infant vomited its feedings. Laboratory findings were as follows: Hemoglobin, 13 gm. per 100 cc.; red blood count, 4.5 million per cu. mm.; white blood count, 9,500 per cu. mm.; 2 normoblasts per 100 white blood cells on the smear. The stool was yellow green and negative for blood. Bleeding, coagulation and prothrombin times were normal. The infant's red blood cell fragility was normal. Both the mother and the baby were Rh positive.

Following a fall in hemoglobin, with a twice-repeated rise after transfusion and subsequent fall, the case was referred for further study. Results showed that the patient's anemia and poor response to transfusion were due to sensitization of the mother (group O) to the infant's erythrocytes (group B). The Rh factor was not involved. When 2 small transfusions of group O red cells (plasma free) were recommended and administered, the infant made an uneventful recov-

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role in the pathogenesis of the disease. The efficiency of sensitization in Rh-negative individuals depends in part upon the amount of Rh-positive blood inoculated into the body. While most may be readily sensitized by properly spaced injections of as little as 2 cc. of Rh-positive blood, isosensitization by pregnancy appears to occur in only 1 out of 25–50 Rh-negative women, perhaps because only minute quantities of Rh-positive blood enter the maternal circulation and at intervals not necessarily optimal for stimulation of antibody production. Another factor is the constitutional ability or lack of ability to be sensitized. Perhaps among Negroids the placenta offers a better barrier, or perhaps the frequency of individuals easy to sensitize is very low.

Injections of soluble A and B substances in small amounts of secretions such as saliva may give rise to sensitization to these factors, while corresponding doses of red cells containing these substances are inadequate to sensitize. Therefore, passage of soluble materials from fetus to mother may give rise to A and B sensitization under conditions which would not be adequate to cause Rh sensitization.

ery. When seen again at the age of 7 weeks, the infant had gained weight and had no jaundice.

The 2nd case involved a mother pregnant for the 4th time. The 1st and 2nd pregnancies had resulted in normal infants. The 3rd pregnancy terminated at 8 months with the birth of an infant who became jaundiced at the age of 3 days. The jaundice subsided and the child was taken home, but later lost weight, and in spite of transfusion developed jaundice and died. Results of blood studies on the parents and 2 living sons showed that the Rh-Hr types had nothing to do with the problem. Titration findings supported the diagnosis of erythroblastosis as the cause of death of the 3rd infant, but with the B factor as the sensitizing agent. The father's group was B, the mother's O, and 1st son's B, and the 2nd son's O; the 1st child must have sensitized the mother, while the 2nd escaped because it belonged to group O. If the expected 4th infant belongs to group O (50 per cent chance) it will not be erythroblastotic. If, however, it belongs to group B it will almost certainly have the disease. In such cases, the prophylactic injection of soluble A and B group substances into the infant by way of the umbilical vessels at the time of birth may serve to ameliorate the disease.

In the 3rd case, following an uncomplicated pregnancy, the infant weighed 5 pounds 9 ounces at birth and was lethargic, pale and appeared to have difficulty in breathing. A bradycardia of 110 beats per minute was present. There was no apparent jaundice, nor discolor of amniotic fluid or vernix. Blood count showed hemoglobin of 7.7 gm. per 100 cc. with a red cell count of 2.32 million per cu. mm., a white cell count of 86,000 per cu. mm., and 82 nucleated red blood cells per 100 white cells on the smear. Studies disclosed no known factor present in the infant's erythrocytes that was lacking from the mother's and no sensitization possible to the A, B, or Rh-Hr factors. Other tests, including numerous sickling preparations, were negative.

Transfusion to combat the anemia was indicated. Since the case might be one of isosensitization against a blood factor as yet undiscovered, it was decided to use the mother's washed red cells, because her erythrocytes could not contain the hypothetical immunizing factor. Hemoglobin rose following transfusion of the washed red cells from the mother's blood resuspended in saline. Two days after birth jaundice was found to be present, hemoglobin had fallen from 15 to 11 gm. per 100 cc., and the proportion of nucleated red blood cells had greatly increased. A 2nd transfusion with washed red cells was done, following which there was a prompt increase in hemoglobin to 15.5 gm. and gradual improvement in other findings. The child was discharged at the end of the 4th week weighing 5 pounds 9 ounces, with a hemoglobin of 10 gm. per 100 cc. and a red cell count of 2.85 million, with no jaundice. Four weeks later she weighed 8 pounds 1 ounce. Her hemoglobin had fallen to 9.1 gm. and her red count was 2.9 million, but otherwise she seemed well.

If the Rh factor played the same role in all races as it does in the Caucasian, one might expect an incidence of erythroblastosis among Negroids from $\frac{1}{3}$ to $\frac{2}{3}$ as high as in Caucasians; however, erythroblastosis does appear to be rare among Negroes, indicating that considerations other than the Rh type play an important

ing will continue unless active treatment is instituted; the first consideration must be prevention of needless blood loss. Also, unnecessary blood loss may lead to anemia, puerperal sepsis, thrombophlebitis, or embolism.

In 32 cases both time and developing hemorrhage were involved. Other indications for manual removal were contracted cervix or pathological contraction ring, placenta partly adherent or fragments retained, retained fetal membranes, marginal or central placenta previa, fibromyomas of the uterus, and severe anemia.

There were no deaths in these 89, and the incidence of postpartum complications was 4.5 per cent, only a fraction of that in the smaller group.

Manual removal is indicated early in cases of progressing postpartum hemorrhage and in cases unassociated with excessive blood loss in which the placenta has been retained for at least an hour. It should be done with a rigid aseptic technique, and antibiotics or chemotherapy should not be relied on to combat a needlessly incurred infection. If removal is deferred for an unduly long time, complications are likely. Manual removal under favorable conditions is comparatively safe, but if it is done as a last resort where severe anemia and contamination have occurred, the incidence of complications may be high. 5 tables.

THERAPEUTIC ABORTION BY MEANS OF SOFT-SOAP PASTES

H. H. FOURACRE BARNS

University College Hospital, London, England

For therapeutic abortion the University College Hospital uses the following paste, sterilized in the autoclave: stearic acid 10 per cent, arachus oil 20 per cent, alkaline solution (potassium hydroxide 9.5 parts, sodium hydroxide 3.75 parts, and water to 100 parts) 20 per cent, "Lanette wax sx" 1.5 per cent, chlorocresol 0.05 per cent and water to 100 per cent.

The patient is prepared for a vaginal operation and given "Omnopon" gr $\frac{1}{3}$ and scopolamine gr. $\frac{1}{150}$ an hour before operation. In the theater, the patient is placed in the lithotomy position. Anesthesia is not needed. The vulva and vagina are cleaned with a solution of "Dettol." After bimanual examination to confirm diagnosis and determine uterine position, the cervix is exposed, grasped with sponge-holding forceps, and again painted with the dettol solution. The sterile paste, at 100°F., is injected into the lower uterine cavity by 20 ml. syringe and a Forsdike's intra-uterine tube. The tube is inserted just through the internal os, without touching the vaginal walls, and the paste is injected about 5 ml. per minute without any force. The tube is withdrawn and the cervix inspected to see that the paste does not return. About 5 ml. plus 1 ml. for each

OPERATIVE OBSTETRICS

MANUAL REMOVAL OF THE PLACENTA

ROBERT W. DEVOE AND ARTHUR B. HUNT

Mayo Clinic, Rochester, Minnesota

In recent years the incidence of postpartum complications and the mortality rate following manual removal of the placenta have been lowered, undoubtedly due to asepsis and chemotherapy. A 20-year study reported in 1937 showed a corrected mortality rate of 2.6 and a morbidity rate of 31.5 per cent. In a recent study of 45 cases complications were eliminated and mortality rate decreased to 0.

In 1936–1945 inclusive, 6753 obstetric patients were treated at the Mayo Clinic. In 98 (1.3 per cent) the placenta was removed manually, and in 2 of these such procedure had been necessary before.

In manual removal, the patient is redraped and the obstetrician puts on a fresh sterile gown and elbow-length sterile gloves. Ethylene and oxygen is usually satisfactory anesthetic but ether is occasionally necessary. The vulvar region and the vagina are prepared again with a liberal amount of antiseptic solution. When the hand is in the uterine cavity, the fundus is brought anteriorly and held with the other hand on the anterior abdominal wall. A cleavage plane is sought between the placenta and the uterine wall, and dissection is done carefully downward so that the uterus can contract over the hand as removal progresses, lessening the amount of bleeding and the danger of perforation.

In 70 per cent of the cases the uterine cavity was packed with iodoform gauze after removal of the placenta, the pack acting as a tampon, stimulating contractions, and carrying small bits of decidual tissue or debris with it when removed.

In 9 cases the patients had received obstetric treatment or repeated vaginal examinations before being brought to the clinic. The placenta had been retained a long time, hemorrhage had occurred, or there had been opportunity for contamination. One of these (in 1936), a patient with a multiple pregnancy on whom several vaginal examinations had been done before admission, died 10 days after delivery, of puerperal sepsis, septic thrombophlebitis of the pelvis, and bronchopneumonia. The incidence of postpartum complications in this group was 77.8 per cent.

. Among the remaining 89 in whom manual removal was done under favorable conditions, in 21 cases the placenta was removed because of prolonged retention averaging 68.8 minutes. In 3 cases loss of blood, averaging 583.3 cc., was the cause for removal. It is felt that in most cases of postpartum hemorrhage bleed-

SOCIAL AND LEGAL ASPECTS

CHILD UPHELD IN RIGHT TO SUE FOR PRENATAL INJURIES

Baltimore Evening Sun

May 13, 1948

Lima, Ohio, May 13 (AP)—A child has a right to sue after birth for prenatal injuries, the Ohio Third District Court of Appeals held yesterday.

The decision was handed down in a $50,000 damage suit filed for Mina Margaret Williams by her father against Marion Rapid Transit Company, Marion, Ohio.

LOWER COURT REVERSED

The appeals court reversed a ruling by the Marion Common Pleas Court that Ohio law does not allow for recovery of damages for prenatal injuries to an unborn child.

However, since this decision is in conflict with one by the Seventh District Appellate Court, the Third District Court certified the case to the Ohio Supreme Court for review.

The petition contended that on April 4, 1941, the plaintiff, although unborn, was capable of living. On that date, the petition said, the mother, Ruth Williams, was a paying customer on a Marion bus.

3 JUDGES CONCUR

Negligent operation caused her to fall on the steps, the suit continued, adding:

Mrs. Williams suffered injuries which caused her death and the 2-month premature birth of the plaintiff. Injuries from which the baby suffers, it was claimed, were a direct result of the mother's fall and the premature birth.

Judge Walter S. Jackson wrote the opinion, with Judges Charles A. Guernsey and George S. Middleton concurring.

week of pregnancy is suggested. A few hours after operation the patient is given 1 or 2 ounces of castor oil.

In the present series of 71 cases indications for abortion were largely pulmonary and cardiac conditions in which inhalation anesthesia was to be avoided. In 56 (nearly 80 per cent) the method was successful without other operative procedures needing general anesthesia; a few needed ecbolics for completion. In 7 cases the paste had no effect at all, and in 8 cases operative procedures with general anesthesia were needed to finish an incomplete abortion. On an average, abortion can be expected to begin 24-48 hours after injection of the paste. The figures, though not statistically significant, suggest less likelihood of success after the 16th week of pregnancy.

In a patient not included in this series, the paste mixed with an equal quantity of "Neohydriol" was inserted and x-rays were taken which indicated that the uterine contractions during the expulsion may drive the paste along the fallopian tubes, showing some paste in the uterus and the left fallopian tube after abortion and in the pelvic portion of the peritoneal cavity 4 days later.

There were no fatalities in this series, nor any hemolysis, pulmonary embolism, or perforation of the uterus. In 3 patients pyrexia followed introduction of the paste (1, seen a year later, showed no abnormality on pelvic examination), while in 3 others it followed procedures used when the paste had been unsuccessful. In some patients temperature rose to 99°F. but fell to normal after the abortion In the few patients followed up, no case of sterility has been noted; 4 became pregnant again, and 2 later sterilized by tubal resection showed no evidence of tubal inflammation. Nevertheless the x-ray evidence suggests a risk of chemical salpingitis and subsequent sterility.

In 4 patients there was heavy blood loss over the 2–8 weeks following abortion, and in 1 of these dilatation and curettage was necessary. This bleeding may be due to a hyperemic reaction of the endometrium to the chemical irritation of the paste. In 2 cases, where abortion was incomplete and hemorrhage followed, later dilatation and curettage removed small pieces of placental tissue.

The method is not intended to replace those where an urgent and immediate evacuation of the uterus is required. Morbidity appears no greater with the paste than with vaginal evacuation or with abdominal hysterotomy, the alternatives most frequently used. Where other things are equal, vaginal digital evacuation of the uterus and the soap paste method are both preferable to abdominal hysterotomy; and abdominal hysterotomy, being more dangerous to life than these other methods and also than sterilization alone (by abdominal resection of the fallopian tubes), should not be chosen solely on the grounds that sterilization can be performed at the same time. 3 figures, 3 tables.

need have a negligible incidence of failure. One of the highest numbers of failures was found in the group of vaginal surgery, usually a vaginal plastic in combination with tubal ligation from below. The difficulties in exposure and approach are obvious. The 24-hour postpartum group also had a rather high incidence; this is the group handled primarily by the senior resident, as are ligations incident to cesarean section. There were no failures in 93 ligations in combination with laparotomy for gynecological indications. One wonders whether the tube altered by normal pregnancy tissue change is less amenable to permanent closing, or so edematous and friable that greatest delicacy is needed to prevent cutting or shearing and subsequent fistula. Morbidity in the series of failed ligation was very similar to over-all morbidity for cesarean sections and vaginal deliveries.

The minimum period between ligation and subsequent pregnancy has been 2 months, the maximum 39 months, averaging 14. Fertility ranged from 2 to 9 pregnancies. Lactation was not significant. Age ranged from 20 to 43 years.

If the operative technique of tubal ligation has been carefully explained to the patient and her husband, there will be no psychic changes and no loss of libido. The menopause will not develop at an earlier age if the venous return from the ovary and tube is not obstructed.

If properly carried out, the Madlener technique, it is believed, will prevent future pregnancies. It is the simplest and safest surgical procedure, and can be performed at the time of a gynecological operation, at the time of cesarean section or abdominal interruption of pregnancy, or as the 24-hour procedure as advocated by this clinic. 1 figure, 3 tables.

SURGICAL STERILIZATION IN WOMEN

Charles B. Darner

Fargo, North Dakota

There is no technic of sterilization without failure; female fertility has an amazing persistence, and even supravaginal hysterectomy has been followed by pregnancy.

In the present group of 238 patients over the period 1936–1946, 121 were Protestant, 62 Catholic, 1 Jewish, and the remaining 54 undetermined. The majority of these, 190 cases, had postpartum tubal sterilization, a procedure described by Whitacre as simple, safe and relatively bloodless. Of the rest, 35 were sterilized incident to pelvic surgery and 13 had therapeutic abortions and tubal sterilizations.

Both the husband and the wife should of course have a complete understanding of the implications of the operation and should give signed permission. Wood-

MISCELLANEOUS

PREGNANCY FOLLOWING TUBAL STERILIZATION

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University of Chicago, Chicago, Ill.

The only certain method of preventing conception is the complete removal of ovaries, tubes and uterus. There are various methods of sterilization, of preventing conception without interfering with ovarian function, the simplest being to block the lumen of the Fallopian tubes. However, the number of failures seems to be large.

This report includes all the cases at Chicago Lying-In Hospital in which various methods of sterilization were used, and the number of failures with each. In most cases, the tube was clamped close to the uterus, using until 1944 a heavy Kocher clamp and from 1944 to 1946 a Payr clamp, and then ligating with a silk suture below and above the crushed area of the tube. Since early 1946 the original Madlener technique has been followed: crushing the tube in the proximal end of the outer third, and placing 1 silk or cotton suture in the area of the crush as well as tying through the crushed area. The tube has been crushed for 1 minute; Madlener did not specify his length of time. The widest part of a Payr clamp which tapers from 8 mm. to 3 mm. has been used, compared with Madlener's angiotribe of 7 mm. width.

None of the patients ligated since 1946 has returned pregnant. No enlargement of either tube has been noted in those patients who became pregnant after ligation and were again subjected to operation. Perhaps there are changes in the tube adjacent to the uterus if ligation is in the outer third, but if so, those changes should increase the safety of the tubal ligation. Crushing and ligating the tube near the fimbriated end and then injecting either 95 per cent alcohol or sodium morrhuate into the wall of the tube adjacent to the uterus certainly adds to the safety of the operation.

While no attempt has been made to follow all patients whose tubes were ligated, it is believed that few failures have been missed, for such patients nearly always return, like a customer who "wants her money back." In those who returned for a subsequent laparotomy, the failures could be ascribed to mistaken identity (1 case, where the round ligament was ligated), or to cases where the tubes were ligated but the lumen re-established, presumably as a result of an excessive constriction of the ligation which had either sheared or completely severed the tube.

Among 912 Madlener sterilizations, failures amounted to 3.6 per cent. The higher incidence of failures among those handled by resident staff in this teaching hospital, as compared with private patients, suggests that the competent surgeon

Maternal Mortality Reports

CASE NO. 58

The patient was a 21 year old white primigravida, whose last menstrual period had begun on November 23, making her EDC August 30. She received prenatal care from her physician and except for the fact that the child was found to be presenting by breech, no abnormalities were noted. On September 18, when she was approximately three weeks past her EDC, she was admitted to the hospital in mild early labor. She remained in the hospital for 72 hours, during which time her uterine contractions were weak and irregular and eventually ceased entirely. The patient was discharged undelivered on September 22. She was readmitted to the hospital in active labor on September 30. Examination at this time revealed a large child presenting by breech, with the presenting part not in the pelvis. A flat plate of the abdomen confirmed the presence of a breech presentation, and the pelvis appeared normal in size and shape.

At this time a consultant saw the patient and advised allowing another 12 hours of labor. Twenty-four hours were allowed to elapse and apparently no progress was made. The exact dilatation of the cervix, station of the breech, and whether or not the membranes had ruptured, are not known. At this time, after approximately 36 hours of labor, the patient was delivered of a living infant by classical cesarean section. The birthweight of the infant is unknown.

On the first postoperative day the patient's temperature rose to 102°, and there was moderate abdominal distention. The patient was treated by constant gastric suction, rectal tube and intravenous fluids. On the second postoperative day the temperature was lower and the distention less marked. On the third day temperature was normal and the abdomen flat. The following day the temperature rose again to 102° and penicillin therapy was begun. From that point on the patient's course was rapidly downhill, with high temperature, abdominal distention and obvious signs of generalized peritonitis. In spite of penicillin therapy, sodium sulfadiazine, plasma, and intravenous fluids, the patient succumbed on the 7th postpartum day.

Comment: There is general agreement that the performance of a classical cesarean section after a patient has been in labor or the membranes have been ruptured for any appreciable period of time, carries with it a considerably greater hazard to the mother than the low cervical type of operation or the extraperitoneal approach. In this particular instance the committee felt that the first fundamental error made in the handling of this case was in choosing the classical type of operation. There was also a regrettable delay in instituting chemotherapy. The patient's temperature went to 102° on the day after delivery, and yet penicillin was not started until the fourth postoperative day. Lastly, blood transfusion was not employed as supportive therapy.

ward states that consent may be invalid because (1) it undertakes to authorize an unlawful act or an act contrary to public policy, or (2) because it comes from a person who has no lawful right to give consent, or (3) because it was obtained by misrepresentation or fraud. Tubal ligation is presumably done for medical indications, including cesarean section, toxemia of pregnancy, cardiac disease, nephritic disease, difficult labors, varicose veins, thrombophlebitis, previous pelvic operations, tuberculosis, diabetes, psychiatric indications, eugenic reasons, hypertension, carcinoma, and excessive multiparity.

If one plots a curve based on the incidence of complications as related to parity, it is shown that there is a sharp elevation in the curve after 4 children. Hence the authors (without taking any of the causative factors into account) hold that multiparity of 4 or more constitutes ample medical indication. Half of their cases were based on multiparity. The next most frequent indication was pelvic surgery without removal of uterus, tubes or ovaries, in 35 cases.

The Madlener method was used extensively in the early cases. In 2 of 4 failures investigation showed that the silk used as suture material had cut through the tube and formed an anastomosis and the tube had reestablished its patency. After a change to the Pomeroy method and the use of plain catgut suture material, there was no failure in 141 consecutive cases. Lull's description of the Pomeroy technic is quoted: "The procedure consists simply in picking up the middle portion of each Fallopian tube, ligating it with an absorbable suture and then resecting the loop. The importance of using an absorbable suture cannot be stressed too much, because when one uses silk ligature the chances of fistula formation are unquestionably increased. Practically no bleeding occurs, although when doing this by the vaginal route, some tearing may occur and give rise to moderate hemorrhage. The cut ends of the tube are drawn apart and the plastic exudate of the perineum becomes organized in such a manner that it does not seem possible for a fistula to occur. Both ends of the tube shrink up to very narrow strands." A dry technic has advantages, but not in tubal sterilization.

In the absence of pathology in the ovaries, tubes or uterus, these should not be removed, particularly before the woman is 40. Removal of tubes interferes with blood supply to the ovaries, with the likelihood of cystic disease of the ovary and symptoms of menorrhagia.

Early incisions were transverse, but recently midline incisions, only 3 cm., have been used.

Of the 190 postpartum tubal ligations, the great majority were done on the day of delivery, and only 1 as late as the 7th day. There was morbidity in 20 of the total 238, unrelated to the day of operation, and no mortality. Operation should be done as soon as possible after delivery. Some were done immediately, under the same anesthesia, when caudal anesthesia was used; most were done under sodium pentothal, and a few under local anesthesia. Length of stay in hospital was not increased.

CASE NO. 60

The patient was a 23 year old white primigravida, whose EDC was February 18. She received routine prenatal care from the second month of pregnancy and no abnormalities were noted at any time. She fell into labor spontaneously on February 14, and was admitted to the hospital at 10:00 a.m. Labor progressed satisfactorily and at 11:15 p.m. on February 14 the patient was fully dilated with the head in the perineum. During labor, however, the patient received by error a bowl of soup containing a considerable quantity of solid food. The patient was anesthetized with ether and a living infant easily delivered by low forceps and episiotomy. After the anesthetic had been discontinued, the patient vomited, aspirated, became cyanotic, and died within a few moments. An autopsy was obtained which showed asphyxiation secondary to aspiration of gastric contents. The bronchi and trachea were filled with many particles of solid food.

Comment: This was the second case of death due to aspiration of gastric contents reviewed by this committee in a single year. In each instance the patient had received solid food during labor. This death was voted preventable, not on the part of the attending physician, but due to improper nursing care during labor. It should be emphatically impressed upon the nursing staffs of all hospitals that patients in active labor are not to receive solid food.

CASE NO. 61

The patient was a 31 year old white para 2 with 2 living children, who was admitted to the hospital September 2 following spontaneous premature rupture of the membranes. Her EDC was October 12. On admission the patient was not in labor and the membranes were ruptured. Her pregnancy to this point had been completely normal and uneventful. She remained in the hospital under observation and her course was uneventful until September 10, at which time the temperature went to 101°, and she was started on penicillin. On September 11 she fell into labor spontaneously and after a short easy labor was delivered spontaneously of a living premature infant weighing 4 lbs. 4 oz. The infant had an unpleasant odor but was otherwise in good condition. The placenta separated spontaneously and was expressed without difficulty 10 minutes after delivery of the infant. There were no perineal lacerations and the patient received 1 ampule of ergotrate intramuscularly. She bled steadily for the next 15 minutes and lost an estimated 500 cc. of blood. She was given another ampule of ergotrate intravenously and the uterus contracted well and vaginal bleeding ceased. She was seen by her physician ½ hour later and the uterus was firm and the patient's condition considered good. A nurse was left in charge of the patient. One-half hour later the physician was recalled to the hospital and upon his arrival there found the patient dead following a massive vaginal hemorrhage.

Comment: The first hour or two following delivery constitute a critical time and it is of vital importance that recently delivered patients be left in charge of competent attendants. Furthermore, it is generally agreed that estimating blood loss is extremely difficult. It is quite probable that this patient lost more than 500 cc. of blood before the physician left the hospital. In any event, he should have made careful observations of the patient's pulse rate, blood pressure, and some effort to replace the lost blood volume. Instead, these observations were not made, nor did the patient receive any sort of supportive therapy. Patients who exhibit any form of unusual bleeding following delivery should be watched with extraordinary care and blood should be available for immediate transfusion.

On the above grounds the committee felt that this was clearly a preventable death.

In summary then, the committee felt that if a low cervical section had been done, and if chemotherapy had been begun at the time of section, or preferably before section, the outcome would probably have been quite different. There is not enough information available to form an opinion as to the justification for carrying out cesarean section.

CASE NO. 59

The patient was a 29 year old white multipara with 2 living children, whose EDC was October 5. She did not consult a physician during her pregnancy until the onset of the present illness. On August 7 the patient fell down the steps at home and shortly thereafter began to have moderately profuse vaginal bleeding. She called her physician, who found the blood pressure to be 118/70, the urine negative, and the patient having rather profuse vaginal bleeding. She was immediately transferred to the hospital with a diagnosis of probable placenta previa. On admission to the hospital on August 7, the patient was in shock, and was given intravenous plasma and glucose and was grouped and matched for transfusion. A stillborn infant was delivered vaginally shortly after the patient's admission to the hospital. Following delivery of the infant the placenta could not be expressed. An attempt was made to carry out manual removal of the placenta but this too was unsuccessful. During this time the patient was receiving blood, plasma, and other intravenous fluids but remained in shock and continued to bleed. A second physician was called in consultation and attempted to remove the placenta manually. This was found to be impossible because the placenta was densely adherent to the uterine musculature. Blood and plasma were continued, but the patient remained in profound shock. Vaginal bleeding continued and abdominal supravaginal hysterectomy was carried out with the patient practically moribund. The patient died in shock and pulmonary edema 4 hours after the performance of hysterectomy. In all the patient was given 3500 cc. of blood, 4500 cc. of plasma, and 4000 cc. of glucose intravenously during her hospitalization.

The specimen removed at operation was examined by a pathologist and was diagnosed placenta previa and placenta accreta.

Comment: The combination of placenta previa *and* placenta accreta is an extremely rare one. With a patient being admitted in profound shock with such a malignant combination of conditions, the chances of a satisfactory outcome are admittedly small. The only criticisms concerning the handling of this case were as follows:

It is noted that the patient received a total of 12,000 cc. of fluid during the short time prior to death, and it was the opinion of the members of the committee that patient was definitely overtreated in this regard, thus placing a great burden on her heart. The addition of 4000 of glucose and 4500 cc. of plasma to the ample quantity of blood being given was unnecessary.

Secondly, the outcome might have been altered had the patient been subjected to cesarean section instead of vaginal delivery, although from the data available this is admittedly questionable. Apparently the patient delivered shortly after admission to the hospital, but the details as to the method of delivery are vague. Presumably version and extraction was performed possibly after manual dilatation of the cervix. If such was the case, and the patient was in reasonably good condition, cesarean section would have been preferable. The death was voted preventable with extremely extenuating circumstances, largely on the basis of the excessive amount of intravenous fluids.

On admission to the hospital the patient was in a state of complete exhaustion. She was given intravenous fluids and plasma, and when her conditon had improved somewhat she was given ether anesthesia and the delivery of a 12 lb. 14 oz. stillborn infant was easily completed at 1:40 a.m. November 16. Following delivery of the child a large amount of very foul smelling material escaped from the uterus. There was no excessive vaginal bleeding immediately following delivery of the infant and placenta, and her immediate postpartum condition seemed satisfactory. At 9:00 a.m. November 16 her blood pressure suddenly fell to 76/40, and she was grouped and matched and given a blood transfusion. Following this the blood pressure rose to 130/70, the uterus was noted to be firm, and there was no excessive vaginal bleeding. During the succeeding two hours, however, the blood pressure fell again, and in spite of repeated blood transfusions, respirations ceased at 1:45 p.m. November 16.

Comment: The committee did not discuss in any detail one of the major problems which a case of this type raises, namely, that of home deliveries by untrained midwives. This involves many considerations, discussion of which space does not permit, such as the responsibility of local physicians, health departments and hospitals in their relation to the untrained midwife. It was the opinion of the committee that even with the tragic events leading up to this patient's admission to the hospital, that her death was a preventable one. With the foregoing history of repeated vigorous attempts to deliver the shoulders, rupture of the uterus should have been a prominent thought in the minds of those handling her following admission. In spite of the foul lochia following delivery of the child and placenta, and in spite of the fact there was no excessive external bleeding, immediate exploration of the uterine cavity should have been carried out. Although no autopsy was obtained in this case, the members of the committee felt that the likelihood of death being due to rupture of the uterus was extremely good. The death certificate on this patient gives the principal cause of death as ruptured uterus, and hence, it is apparent that the diagnosis was not made until the patient had gone into profound shock some 7 hours after delivery.

CASE NO. 62

The patient was a 35 year old colored para 4 with 4 living children, whose EDC was September 21. Pregnancy progressed normally and uneventfully until September 7, at which time the patient was admitted to the hospital with the complaint of painless vaginal bleeding. On admission the patient's general condition was good, blood pressure was 138/85, and an estimated 38 week fetus lay in LOA position with the fetal heart in the left lower quadrant. Hemoglobin was 80%, and the urine negative. A rectal examination was carried out revealing a closed cervix. On September 8 the patient passed several blood clots per vaginam. On that date the red blood count was 2,600,000, and the hemoglobin had fallen to 52%. On September 9 she continued to pass clots. On the following two days there was no further bleeding and the patient had no complaints. On September 12, a contrast film of the bladder was made and read the following day as being "highly suggestive of placenta previa." On September 15 classical cesarean section was performed with the delivery of a living male infant. Blood loss at operation was excessive and the patient was returned to her room in shock. She received multiple blood transfusions following delivery, but in spite of this and other supportive therapy she continued downhill and died on September 17.

Comment: The so-called conservative treatment of placenta previa has gained widespread attention but lends itself readily to misinterpretation. One of the major points made by those who have recommended it is that the blood picture *must* be kept within normal limits. Furthermore, the purpose of temporizing with cases of placenta previa is solely to allow the infant to attain sufficient size to improve its chances of survival outside of the uterus. These two primary considerations were completely overlooked in the handling of this patient. The patient's hemoglobin was 52% a full week before delivery, and yet no blood transfusions were given until after cesarean section. The patient was two weeks from term at the time of admission to the hospital, and there was nothing to be gained by postponing treatment of her condition for eight days. The diagnosis should have been established or ruled out promptly and an immediate delivery undertaken when the finding of placenta previa was confirmed. This patient should have received several transfusions prior to delivery, and should certainly have been receiving blood at the time cesarean section was started. Another criticism of the handling of this case was the performance of a rectal examination, which often precipitates severe and possible fatal hemorrhage in placenta previa.

CASE NO. 63

The patient was a 28 year old colored para 1 with 1 living child, whose EDC was November 20. Her previous pregnancy and delivery had been normal and uneventful. She was followed prenatally by her family physician who considered her a normal case and allowed her to engage a midwife for delivery. The patient fell into labor spontaneously on November 15, and labor progressed uneventfully. At 12:30 p.m. the midwife delivered the head of the infant spontaneously. The midwife was unable, however, to complete the delivery of the shoulders and the family physician was called. There was a considerable delay in the physician reaching the patient's home and she was not seen by him until approximately 4:30 p.m. He attempted to deliver the shoulders but was also unsuccessful, and arrangements were initiated for transferring the patient to a hospital. Again there was a long delay in obtaining transportation for the patient, and she did not reach hospital until 12:30 a.m. November 16, at which time the infant's head had been delivered for 12 hours.

gists have the feeling that injudicious use of stilbestrol for menopausal symptoms is more likely to produce postmenopausal bleeding than the natural hormones, and that in certain other respects it appears to be even more estrogenic in its effects than are most of the natural hormones themselves.—Ed.)

A COMPARISON OF THE GROWTH OF THE OVUM AND FOLLICLE IN NORMAL RHESUS MONKEYS, AND IN MONKEYS TREATED WITH OESTROGENS AND ANDROGENS

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J. Endocrinol., 5: 207–219, 1947

In this study the regression lines relating the size of ovum and developing follicle were determined for 8 normal rhesus monkeys, 2 monkeys treated with estrogen, and 3 with androgen. No statistically significant differences were found between the regression coefficient for either phase of follicular growth in the 3 groups of animals. Regression coefficients in normal monkeys may vary over a wide range, and it would seem necessary to determine the relationship between size of ovum and follicle in several animals of a species before assigning to the species definite values for this relationship.

Estrogen not only prevents the later stages of follicular development but also causes widespread atresia in the earlier stages of follicular growth. Androgen considerably stimulates healthy development of the early stages of follicular growth, but does not affect the later stages. The influence of estrogens and androgens in the early stages of follicular development appears to constitute a direct effect on the ovaries. 7 figures.

THE ENDOCRINE FACTORS IN PELVIC TUMORS, WITH A DISCUSSION OF THE PAPANICOLAOU SMEAR METHOD FOR DIAGNOSIS

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Radiology, 50: 190–201, 1948

Of particular endocrine interest are the rare functioning tumors of the ovary. Although the histogenesis of these "feminizing" and "masculinizing" tumors is related to certain embryologic factors in the development of the gonad, no endo-

Gynecology

ENDOCRINOLOGY

THE ACTION OF INTRAVENOUSLY INJECTED SEX HORMONES AND OTHER SUBSTANCES ON THE BLOOD FLOW IN THE HUMAN ENDOMETRIUM

A. A. LOESER

In this study the author attempts to elucidate the mode of production of the vascular changes in the human endometrium exposed to the immediate action of intravenously injected sex hormones. For this purpose an instrument was constructed, resembling in principle the apparatus used by Richards, Wolf and Wolff in their studies of the blood-flow in the human gastric mucosa. This instrument is a uterine catheter which records changes of ·blood-flow in the human endometrium. The writer describes the instrument and its method of use.

The substances investigated and the maximum doses used at one intravenous injection were: estrone, 10 mg.; estradiol, 20 mg.; stilbestrol, 150 mg.; progesterone, 100 mg.; testosterone propionate, 250 mg.; adrenalin, 0.1 mg.; prostigmin, 1.0 mg.; pituitrin, 3 units; pitocin, 5 units; calcium gluconate, 20 ml. of a 20 per cent solution; nicotinic acid, 50 mg.

Estrogens in doses of 2 mg. or more produce more or less marked temporary vasodilatation in the endometrium. When the endometrium is poorly developed the response is less pronounced. When the endometrium is completely atrophic no vascular change occurs. Stilbestrol is less active than the natural estrogens. Pitocin is without effect. Pituitrin and adrenalin constrict the blood-vessels rapidly, markedly, and for a long time.

Testosterone propionate generally has a vasoconstrictor effect after an initial temporary dilatation; the degree of vasoconstriction is variable but is not dependent on the phase of the menstrual cycle. The vasoconstriction lasts longer than the vasodilatation produced by estrogens. An itching effect in the external genitals was marked in all cases and was worse when larger doses of testosterone were injected; it disappeared after a few minutes.

(The apparatus used by Loeser as a basis for these studies is an interesting but rather intricate one, which my own unmechanical mind cannot evaluate, and I suspect that this will apply to most other gynecologists as well. However, Loeser has had the collaboration of a competent physicist in its construction, so that the accuracy of the instrument in detecting minute changes in the endometrial blood flow can probably be assumed.

It is of interest to note that, in their effects upon the blood flow as in certain other effects, the estrogens and testosterone propionate are antagonists, the former producing temporary vasodilatation, the latter vasoconstriction. It is also of interest to note that stilbestrol is less active than the natural estrogens in this respect, in spite of the fact that many gynecolo-

attributed in some cases to estrogen therapy. However, the assumption that estrogens cause cancer in man must be considered as not proved for the present. In the human, endocrine dysfunctions, particularly ovarian, have been regarded as a causative factor in the production of fibromyomata, but the evidence is far from conclusive. Perhaps the most convincing evidence is the regression often observed in these tumors in the postmenopausal period, and, conversely, the rapid enlargement of fibroids in patients receiving injudicious estrogen therapy.

The cytologic examination of vaginal smears in the diagnosis of uterine cancer is discussed. The author emphasizes that the method is not intended as a procedure for establishing the diagnosis but rather as a means of finding additional cases that should have the benefit of cervical biopsy and curettage. In spite of some instances of error, careful investigation of patients with suspicious smears has led to the discovery of very early cases of uterine cancer which otherwise would have been overlooked.

At present, 418 of a series of 500 vaginal smear studies have been reviewed from the Gynecologic Wards of the Jefferson Hospital. The results are as follows:

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Total patients...................................................... 418
Patients with cancer of the uterus.................................. 59
    Correct positive smears........................................ 41 or 70%
    False negatives................................................ 17 or 28%
    Doubtful smear................................................. 1 or  2%
Patients who did not have cancer.................................... 359
    False positives................................................ 4 or 1.1%
    Doubtful smears................................................ 5 or 1.4%
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Of the 41 patients with smears positive for cancer, 37 had cervical cancer. Of 4 fundal carcinomas, 2 were correctly diagnosed by vaginal smears and 2 were missed. The author's experience with the vaginal smear method thus far leads to the belief that the procedure is sufficiently worthwhile to be made a routine part of the examination on a gynecologic service, although it is apparent that from single examinations a goodly percentage of cancers can be missed. The best procedure is probably to take smears from both the vagina and cervix. 9 figures.

(I know of no evidence to suggest that the common type of endometrial hyperplasia, as it occurs during reproductive life, has any predisposing influence toward the development of endometrial carcinoma. Only a very few instances of such an association have been reported, and even these are open to question because of the occasional pseudomalignant histological appearance of so-called atypical hyperplasia, not to speak of the factor of mere coincidence.

On the other hand, I believe that the postmenopausal type of hyperplasia may play some predisposing role, as the studies of Novak and Yui, Taylor and others have suggested. I do not believe that Rakoff has sufficiently emphasized the age factor in discussing the possible predisposing role of hyperplasia.

It has always seemed to me that the greater predisposing capacity of the postmenopausal type of hyperplasia may be linked up with the absence of progesterone at this age period, as progesterone does seem to counteract the tumorigenic tendencies of estrogen, and may

crine factor is definitely known to be responsible for their appearance. The possibility of an endocrine influence is suggested by several experiments in which there developed in rat ovaries transplanted to the spleen what appeared to be granulosa-cell tumors. These tumors have been attributed to excessive unopposed gonadotrophic stimulation thought to develop in these animals since the estrogen that normally checks the gonadotrophins is removed by the liver before it can enter the systemic circulation. The granulosa- and theca-cell tumors have awakened interest in recent years in the problem of carcinogenesis because in postmenopausal women they are sometimes accompanied by endometrial cancer, suggesting that the increased estrogens that they produce may be of etiologic significance in the associated lesion.

The writer discusses the relationship of the ovarian hormones and uterine tumors. There have been certain observations to suggest that endometrial hyperplasia in the human may be a precancerous lesion. This evidence may be summarized as follows:

1. Endometrial hyperplasia has been experimentally produced in many species, especially when unopposed by progesterone. In women, it frequently appears at the menopause or in younger women with ovarian dysfunction.

2. The histologic changes vary from proliferation of the endometrium to those simulating early adenocarcinoma.

3. Islands of squamous epithelium are known to occur in the human endometrium and are perhaps the counterpart of the squamous metaplasia developing in animals following estrogen administration. Such metaplasia is sometimes found as an associated lesion in endometrial hyperplasia.

4. According to some observers, pathologic specimens in which carcinoma is found arising in a hyperplastic endometrium are not uncommon.

5. Increasing numbers of cases are reported with an association of granulosa-cell tumor of the ovary and endometrial adenocarcinoma, suggesting the sequence of hyperestrogenism, hyperplasia of the endometrium and, finally, adenocarcinoma.

6. On the other hand, while endometrial hyperplasia is common, endometrial carcinoma is relatively rare, and in long-term observations of many cases with hyperplasia, fundal carcinoma develops in but a few. The available data seem to indicate that endometrial hyperplasia is not ordinarily of itself a precancerous lesion, yet there is some reason to believe that under certain circumstances it may become one.

Experimental cancers of the cervix have been produced by injections of estrogens in one species, the mouse. There are a number of clinical observations which have been thought to suggest an endocrine factor in the development of cervical cancer. It is known to occur more frequently in multiparous women than in those who have not borne children. Hofbauer believed this might result from the intensive stimulation by the rising estrogens titer during pregnancy. In a number of instances, metaplasia of the cervical epithelium has been observed following estrogen administration in women. Cervical polyps have also been

Neither ova nor normal ovarian follicles were observed in any of the irradiated grafts.

Castration and intrasplenic ovarian grafting were performed on 6 male and 6 female mice, and 17 to 56 days later, roentgen irradiation, in a single dose of 400 r, was delivered over the hypophyseal region. One granulosa-cell tumor and 3 mixed tumors developed intrasplenically in the 6 male mice. Among the 6 females there were 3 granulosa-cell tumors, one luteoma and one mixed tumor. Thus, roentgen irradiation of the hypophysis did not inhibit the formation of the intrasplenic ovarian tumors.

Four male and 7 female mice were gonadectomized and the spleens implanted with a pre-irradiated ovary. A single dose of 200 r was delivered to the excised ovaries in vitro. Only 5 of the animals developed tumors at the site of grafting and in general these tumors were smaller than those noted in animals of the preceding experiments.

Two ovaries were implanted in each of 4 male and 2 female mice. One of the ovaries was implanted intrasplenically directly after excision and received no irradiation. The other ovary was exposed in vitro to a single x-ray dose of 200 r, and then implanted either proximal or distal to the first. One of the female mice developed luteomas in both of its ovarian grafts. No tumors appeared in either graft of the other female, or in 2 of the males. The other 2 males exhibited, respectively, a luteoma in the irradiated graft only, and a mixed tumor in the untreated graft alone. In addition, areas of granulosa-cell proliferation of suggestively pre-tumorous character were observed in 2 non-irradiated grafts. Ovarian follicles were not observed in any of the irradiated grafts but were present in both the tumors and nontumorous grafts not exposed to radiation. 10 figures.

(The studies reported in this paper represent one of the most interesting and provocative new developments in tumorigenesis, in general, with obvious special bearing on our ideas as to the histogenesis of granulosa cell tumors. The fact that such tumors develop in intrasplenic ovarian implants would seem to suggest that the destruction by the liver of estrogen produced by the ovarian tissue planted in the spleen is an important factor. Indeed, the hypothesis has been advanced that it is the thus unopposed action of the pituitary gonadotrophes which is responsible for the production of the ovarian neoplastic response.

The original rather materialistic explanation of Robert Meyer, that human granulosal tumors were simply neoplasms arising in redundant granulosal rests left over in the early stages of folliculogenesis, has long been questioned on various grounds, and the origin of both granulosal and thecal cells referred back to the ovarian mesenchyme of a pregranulosal and prethecal stage.

But such studies as those mentioned above link up the origin of such tumors much more directly with a possible inciting endocrine factor, and offer a fascinating new vista for those who still feel that the closed door of many tumors, including even cancer, will some day be unlocked with an endocrine key, to borrow the picturesque phrase of the late James Ewing. —Ed.)

thus exercise a protective influence upon the endometrium of women in the menstruating years. This protective role of progesterone is well shown in the classical studies of Lipschütz and his coworkers upon guinea-pigs. While estrogen administration in large dosage and for long periods brings about the formation of even large and multiple tumors in the connective tissues of the pelvis and abdomen, the simultaneous administration of progesterone prevents such tumor formation. Or, if such tumors are produced by estrogen alone, they may be made to disappear quickly through the administration of progesterone. These studies cannot of course be applied to the question of carcinogenesis, but they are at least suggestive.

Both the vaginal and cervical squamous epithelium are responsive to the estrogen, but the hormonal changes in the cervical squamous epithelium have not been as thoroughly studied as have those of the vaginal epithelium. I mention this because I believe that some of the lesser degrees of epithelial and so-called basal cell activity now being so widely discussed in connection with precursory stages of carcinoma may actually be due to cyclical estrogen effects. We are now studying surface curettings of the cervix in the hope that some light may be thrown upon this problem. As for such lesions as cervical polyps and myomas, the evidence for a hormone causation seems to me to be very flimsy.

The author's reported results with the vaginal smear method in the diagnosis of cancer indicate a considerable degree of fallacy, especially in the large proportion (28 per cent) of false negatives in patients with actual cancer. If even a trained cytologist, like Rakoff, encounters such a high percentage of errors, one can imagine the fallacy of the method in the hands of the many imperfectly trained men who are now using the method. All of which reinforces the growing feeling that, while vaginal smears may prove to have a valuable screening role, they cannot have the decisive value of the tried and true method of biopsy. Moreover, there are far more good pathologists in the country than there are expert vaginal cytologists.—Ed.)

EFFECTS OF X-RAY IRRADIATION ON THE DEVELOPMENT OF OVARIAN TUMORS IN INTRASPLENIC GRAFTS IN CASTRATED MICE

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This paper presents some results of experimental attempts to influence, by roentgen irradiation, the development of tumors in ovaries grafted into the spleens of castrated mice, and to detect, if possible, any synergistic action of these 2 tumorigenic stimuli.

Eight male and 9 female mice were castrated and an ovary grafted into the spleen of each. Eight to 52 days later, roentgen irradiation in a single dose of 400 r was administered over the splenic area. All 8 male mice developed ovarian tumors, 5 of which were of the granulosa-cell variety, while 3 exhibited a mixture of granulosa and luteinlike cells. The 9 female mice yielded 7 ovarian tumors; 3 were luteomas, and 2 each were of the granulosa-cell or mixed varieties. The incidence and time of origin of these tumors were not modified by irradiation.

HORMONAL ALTERATION OF ADVANCED CANCER OF THE BREAST

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Bull. New England M. Center, 10: 1-6, 1948

The author feels that there is considerable evidence which suggests that the sex hormones are factors in the genesis and regulation of breast cancer. Beneficial effects may follow castration in patients with advanced cancer of the breast. Favorable responses are manifested by relief of pain, improvement in physical status, increased hemopoiesis and apparent regressions of osseous and pulmonary metastases. Benefits following castration are confined almost exclusively to premenopausal patients.

Experimental evidence has been accumulated concerning the role of sex hormones in cancer of the breast. Ovariectomy results in marked reduction in the incidence of spontaneous mammary cancer in mice having a high susceptibility to the disease. Moreover, breast cancer can be induced in male mice of certain strains by the administration of estrogens, and androgens may significantly reduce the percentage of spontaneous breast cancer in female mice of a highly susceptible strain.

It would appear that significant alterations in this disease occur after androgen therapy. The most obvious favorable effects are on the osseous metastases and the physical status of the patient. Beneficial results have been observed in both the pre- and postmenopausal group. However, acceleration of the osseous disease has been experienced in some instances.

It is of considerable interest that in certain cases benefit is derived from estrogenic therapy. In most cases there is little change in the osseous development of the disease, but there may be improvement both locally and in the patient's general status. Improvement, in general, is confined to those patients over 60 years of age, and acceleration of the disease has occurred in women of the premenopausal group.

Cancer of the breast in males has also responded favorably to hormonal therapy in some instances. Estrogenic substances and castration have been advocated. Unlike breast cancer in the female, the best response in males over 60 years of age seems to follow castration.

The author points out that sex hormones may profoundly alter the course and character of advanced cancer of the breast in certain patients. However, the mode of action is subtle, especially since even with the same form of therapy there is considerable variability in the effects on different patients. The mechanism by which the different forms of hormonal therapy bring about changes in cancer of the breast is unknown. There is no real evidence that the administration or

INHIBITION OF ESTROGEN-INDUCED TISSUE GROWTH WITH PROGESTERONE

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The observations reported in this paper are concerned with the quantitative characterization of estrogen-progesterone antagonism and with some initial biochemical studies aimed at elucidating the mechanism of this antagonistic action.

Three-week-old New Hampshire Red chicks were used for the study. Stilbestrol was administered daily subcutaneously in 0.1 cc. corn oil, and progesterone was administered similarly in 0.2 cc. corn oil. Autopsies were performed 24 hours after the last of 8 daily injections.

The simultaneous administration of progesterone with either stilbestrol or estradiol resulted in a marked inhibition of the estrogen-induced tissue growth in the genital tract of the chicks. This inhibition was proportional to the dose of progesterone over a limited range. However, once a maximum degree of inhibition was obtained, further increments in progesterone dosage did not effect further decrements in estrogen-induced tissue growth. A 16-fold increase in estrogen dosage did not reverse the inhibitory effect of a maximally effective quantity of progesterone.

The lipemia and calcemia usually seen in estrogenized birds were unaltered by the simultaneous administration of progesterone in doses effecting a maximal degree of inhibition of estrogen-induced tissue growth in the genital tract. 2 figures.

(*It is of interest to note that the same inhibiting effect of progesterone upon estrogen-induced growth which has been demonstrated in a number of other species occurs also in the chick. It is a provocative idea which justifies intensive study. The most spectacular demonstration of this estrogen-progesterone antagonism is furnished by the well-known studies of Lipschütz and his coworkers in the guinea-pig. It will be recalled that these investigators are able to produce large and multiple intra-abdominal fibromatous growths by prolonged estrogen tissue, but not if progesterone is given simultaneously. Again, if such growths are produced by estrogen alone they can be made to melt away rather rapidly by the administration of progesterone. A similar antagonism of the 2 hormones has been shown to occur with the remarkable pseudo-malignant hyperplastic lesions produced by estrogen in the breasts and uteri of various animals.*

Another possible exemplification of this general idea, though obviously still not established, is to be seen in the not infrequent endometrial hyperplasia of postmenopausal women, which many of us believe predisposes to the development of adenocarcinoma. Could this predisposition be due to the fact that at this phase of life the endometrium is no longer under the protective anti-tumorigenic effect of progesterone? It can't be proved, but it is worth thinking about.—Ed.)

ARTIFICIAL REPRODUCTION OF THE CYCLIC CHANGES IN CERVICAL MUCUS IN HUMAN CASTRATES; WITH CLINICAL CORRELATIONS

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Normally menstruating women were studied in order to observe the normal cyclic changes in cervical mucus. In addition, cases with endocervicitis and other lesions were studied. Further, 7 women with only a cervical stump following supravaginal hysterectomy and bilateral oophorectomy were utilized to observe the effects of various steroids upon cervical mucus.

In the immediate preovulatory phase (about days 13 to 15 of an average 28 to 30 day cycle), and synchronous with the so-called "ovulatory dip" or temperature shift in the basal body temperature curve, there occur the following characteristic changes in the cervical mucus: a decided increase in volume, a marked decrease in viscosity, and practically complete absence of polymorphonuclear leukocytes. This clear watery mucus is easily and rapidly penetrable by relatively large numbers of sperm which remain actively motile in it for 24 to 72 hours; a longer time by far than in mucus obtained at any other time of the cycle. These conditions prevail for only about one to 3 days in the average woman's cycle.

These alterations in the cervical mucus, characteristic of the immediate preovulatory or co-ovulatory phase of the cycle, were entirely duplicated in suitable women castrates with only a cervical stump, by the administration of various estrogens, including estradiol and diethylstilbestrol.

In control castrates progesterone alone, as well as testosterone propionate and methyl testosterone, in the dosage used, was not observed to stimulate the flow of cervical mucus.

An essential factor in the increase of the volume of the cervical mucus along with the concomitant decrease in viscosity appears to be an increase in the relative amount of fluid (water?) in the cervical secretions. Sperm penetration and migration were maximal when viscosity was minimal. As a rule, viscosity and volume were inversely proportional.

Following ovulation and with establishment of the postovulatory rise in the basal body temperature curve, the volume decreases markedly, the viscosity increases rapidly, leukocytes once more are noted, while sperm no longer are able to invade the mucus even though they are actively motile for 24 to 48 hours. These postovulatory changes were completely reproduced in estrogen-primed

deprivation of hormones is in any sense a cure for breast cancer.   Thus it is obvious that hormonal therapy should not be substituted for orthodox methods of treatment.   However, it may be effective as a palliative method, particularly when other therapy is not feasible.

(The possible role of the endocrines in the causation of cancer has been one of the hot trails in this field for many years, and no one can say that it has not yielded interesting and provocative results.   Equally interesting have been the applications of endocrine therapy in the management of certain types of cancer.   The first and most shining example thus far has been the use of estrogen in prostatic cancer.   While not curative, it has been an immense boon in the prolongation of life and the mitigation of the suffering of patients with this disease.

Another application of endocrinology has been in the castration or the radiotherapeutic abolition of ovarian function in premenopausal women suffering with mammary cancer. Not all surgeons are convinced of its value, but a large proportion, probably the majority, practice the plan.   Again, the results of testosterone therapy in the palliation of advanced mammary cancer have apparently been encouraging if one can judge from the few reports, like the one from the Memorial Hospital in New York by Adair, which are as yet available. While, as Nathanson says, estrogen has been used by some in the same group of cases, the results seem thus far to be less favorable than those in which the male hormone has been used.—Ed.)

tient wears the drain for a minimum of 2 menstrual periods, being seen several times while the drain is in place. It has not been the authors' experience that the drain is in any way dangerous if the technic outlined is followed.

The procedure has been used in 330 cases from 1933 to 1946, with only one case of very mild infection (0.3 per cent). Careful follow-up and evaluation were possible in 101 cases. Of these, 50 per cent had complete relief, over 30 per cent were greatly aided, and 20 per cent were regarded as failures. Since only the 20 per cent most severe cases were treated by insertion of the Wylie drain, the incidence of failure was only 4 per cent of all cases of dysmenorrhea seeking care.

It is suggested that Wylie drain insertion is the procedure of choice in the severe group of cases, and that presacral neurectomy should be considered only in the few cases which are not relieved by this comparatively minor procedure. 1 figure.

(The use of the stem pessary in the treatment of primary dysmenorrhea has been so widely criticized that it takes a bit of courage to advocate this plan as warmly as has been done by the authors. The senior author, a gynecologist of great experience, has long since demonstrated that he is not lacking in the courage to state his convictions honestly and forcefully, and the results reported in this study would seem to lend support to the stand taken by the authors. On the other hand, I believe that these results are better than those reported by most authors in the days when this plan was much more popular than at present, and the incidence of unpleasant complications lower. A good many serious pelvic infections have occurred from the use of the cervical stem, including at least some which were fatal. Aside from these graver risks, however, my chief objections to the stem pessary, in the days when so many of us employed it, lay in the fact that so many patients with clean, nulliparous cervices were left with a troublesome and persistent cervicitis and leucorrhea, as might be expected from the retention of a foreign body in the cervical and lower uterine canal for a good many weeks. I certainly do not believe that a man should be jailed if he occasionally and circumspectly, in these often highly worrisome patients, resorts to the stem pessary, but I personally would not like to see this plan regain the vogue which it once enjoyed. I do not believe that many would be able to report 330 cases with only 1 of very mild infection.—Ed.)

ROENTGENTHERAPY IN PRIMARY AMENORRHEA

A. BASSAN AND A. PUJADAS

Rosario, Argentina

The author reports a case of primary amenorrhea in a 21-year-old single female, in whom pelvic examination revealed no abnormality of the genital tract. She was put on hormonal treatment (gonadotrophins, estrogens, progesterone and thyroid) without any improvement whatsoever. Short waves applied to the pituitary region, too, yielded no results. Finally the author decided to apply stimulating roentgentherapy to the ovaries (3 applications). Menstruation oc-

castrates by means of either of 2 active progestogens: progesterone and ethinyl testosterone.

In the light of these observations, the author concludes that postcoital studies of sperm migration in the cervical mucus can be of utmost significance only when made in the immediate preovulatory phase of the cycle. For adequate clinical evaluation, this test should be performed on about day 11, repeated on day 14 and if necessary on day 17 of the average 26 to 30 day cycle.

Chronic infection of the endocervix, with or without concomitant erosion, brings about an increased viscosity of the cervical mucus. As a result, infertility may follow because of the hindrance to normal sperm migration.

(It has been definitely established in recent years that at about the time of ovulation there is a marked hyperactivity of the cervical glands, with an increased exudate of lowered viscosity and therefore greater penetrability by the spermatozoa. As a matter of fact, it is not unusual for patients themselves to report a moderate degree of clear, thin mucous discharge at this phase of the cycle, and this is often noted in women entirely free of any cervical infection, and even in virgins. It is just another illustration of the remarkable purposefulness of the events which make up the reproductive cycle, all designed to facilitate the extrusion, transport and fertilization of the egg. Abarbanel's studies are of interest in that the cervical phenomena have been artifically induced in women with no ovarian hormones of their own, thus emphasizing the causal role of these hormones in normal women.—Ed.)

THE STEM PESSARY IN THE MANAGEMENT OF PRIMARY DYSMENORRHEA

E. A. Schumann and M. L. McCall

Philadelphia, Pa.

The vague etiology of primary dysmenorrhea is briefly discussed. The authors consider it likely that these painful uterine contractions are due to a spasm and contraction of the musculo-fascial areas about the internal os. The fact that so many women who have suffered from primary dysmenorrhea in their youth experience complete relief after their first childbirth is highly significant.

The writers agree with the general opinion that about 80 per cent of cases can be satisfactorily treated with conservative therapy (analgesics, hormones, psychotherapy, general hygiene, etc.). In the remaining group with a severe symptom complex, they think that a much simpler procedure than presacral sympathectomy is satisfactory. This procedure is use of the Wylie drain.

The technic and precautions in the use of the Wylie drain in these cases is outlined. The drain is inserted under anesthesia and with careful asepsis, following dilatation of the cervix. The largest drain compatible in the given case should be inserted. Forty-eight hours rest in bed is advised, and the pa-

tient wears the drain for a minimum of 2 menstrual periods, being seen several times while the drain is in place. It has not been the authors' experience that the drain is in any way dangerous if the technic outlined is followed.

The procedure has been used in 330 cases from 1933 to 1946, with only one case of very mild infection (0.3 per cent). Careful follow-up and evaluation were possible in 101 cases. Of these, 50 per cent had complete relief, over 30 per cent were greatly aided, and 20 per cent were regarded as failures. Since only the 20 per cent most severe cases were treated by insertion of the Wylie drain, the incidence of failure was only 4 per cent of all cases of dysmenorrhea seeking care.

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curred for a day, 20 days following the last application. Put on estrogenic treatment for 8 months, the patient menstruated regularly every month. This therapy was then discontinued and menstruation has continued to appear regularly and spontaneously every month for the past $4\frac{1}{2}$ years.

The author discusses this stimulating therapeutic procedure and analyzes the different technics utilized (Edeiken, Kaplan, Siegler and Teperson, Molinari and Diaz, etc.) as well as the results achieved by the various specialists who have resorted to this form of treatment. In his opinion, stimulating roentgentherapy ought to be considered a valuable procedure in the therapeutic armamentarium of the gynecologist.

(The use of x-ray in the treatment of primary amenorrhea has been discussed in these pages on a number of previous occasions, and gynecologists still differ as to its efficacy, its rationale and its wisdom. The chief objection which some urge is on the basis of genetic studies on lower animals, which indicate a harmful effect, not so much on the patient or the immediate offspring, but on the third generation (Little). Whether or not this applies to the human no one is in a position to know, but it is probably this theoretic possibility rather than any other which has made many conservative gynecologists hesitant in the employment of the method.

On the other hand, I know of no important evidence as yet available in the human field to substantiate these fears, and there are a number of reports, including some from gynecologists of high standing, that the method is often efficacious in establishing the menstrual function, although there is considerable variation in the reports as to the frequency of such good results. In spite of the harmlessness of amenorrhea in itself, there are a good many cases in which the psychological attitude of the patient and especially her frequently desperate desire to do anything which might give her at least some chance for pregnancy, not to speak of the usual inefficacy of other methods of treatment, make resort to x-ray seem justifiable. In my own hands, it is only a method of last resort, and not almost of first resort, as it appears to be with some. Whether or how often the individual gynecologist will employ it must depend on his own individual evaluation of the still very inconclusive evidence available on both sides of the question.—Ed.)

VULVA AND VAGINA

CONGENITAL ABSENCE OF THE VAGINA

V. S. COUNSELLER

Mayo Clinic, Rochester, Minn.

J. A. M. A., **136**: 861–866, 1948

In this paper the author reports a group of 76 cases of congenital absence of the vagina, describes a surgical procedure which he thinks is adequate and discloses the results. The embryologic aspects of this anomaly and the historical development of surgical methods for its correction are discussed.

The 76 cases herein reported were seen and treated during the decade ending Dec. 31, 1946. For 70 patients the technic of McIndoe was employed, in which a "lucite" mold, covered by a Thiersch skin graft taken from the abdomen or thigh, was used. For 6 patients, simple reconstruction was done, in which a "lucite" mold was left in the vaginal tract without a skin graft. The patients' ages ranged from 14 to 49 years.

Not all the patients were studied for anomalies of the urinary tract, but of those studied, 16 were normal in this respect and 19 had some type of anomaly. Of the 19, 6 had a pelvic kidney, 5 had a solitary kidney, 3 had duplicated ureters or pelves, 2 had pyeloureterectasis, 1 had a malfunctioning kidney, 1 had a solitary fused kidney and 1 previously had undergone nephrectomy for an unknown reason. Four had incomplete development of the uterus and bilateral hematosalpinx and endometriosis. In each instance there was complete absence of the cervix; hence, abdominal hysterectomy was performed. In one patient in this group the cervical canal was opened when the vaginal tract was reconstructed; this was followed by normal menstruation.

Of the 70 patients in whom skin grafts were used, 55 obtained excellent results, although for 2 it was necessary to do a secondary grafting procedure. For 10 of the patients the result was considered to be fair, since some had granulations which would not epithelialize and produced slight contracture. In 5 cases the results were considered to be poor or failures; they were due primarily to infection, with incomplete take of the grafts, resulting in contracture and stenosis. Three of these patients were uncooperative and refused to wear the mold. Of the 6 patients in whom no graft was used, all have obtained excellent results. The vaginas have completely epithelialized, there are no contractures and the vaginas are of normal depth and normal mobility. Twenty-eight of those heard from are now married and all reported normal marital relations.

McIndoe said that the contraction factor of any canal lined by a Thiersch graft may last 3 to 6 months or longer, and that if the mold is removed before this contraction disappears, stricture of the new canal will result. Most failures

or poor results are due to the removal of the mold too soon.   If the vagina has not been constructed by means of the grafting procedure, a vaginal mold also is required to be worn until the entire tract has been proved by observation and biopsy to be completely epithelialized.   This will require a minimum of 4 months.

In conclusion, it should be said that most histologic evidence indicates that the normal vagina is formed from the müllerian ducts and the urogenital sinus. If there is no evidence of müllerian ducts or epithelial buds from them, the new vaginal tract had best be constructed by means of a skin graft, particularly if there has been much difficulty in dissection.   In other cases, a graft need not be used.

(The results reported in this large series with the McIndoe technic are excellent just as are those reported from the employment of the somewhat similar Wharton operation by others.   Some such procedure as this appears to have established itself as the method of choice in the great majority of cases.   The use of skin grafts covering the various types of vaginal mold appears to be a worthwhile addition to the technic, although with many gynecologists it will have the disadvantage of necessitating the cooperation of a plastic surgeon trained in the technic of skin grafting.

An impressive feature of this study is the high incidence of associated anomalies of the urinary tract, more than half showing some important congenital abnormality, a fact which should never be forgotten in the study of these cases, although such anomalies would rarely contraindicate the operation.   Intravenous pyelography should be practically a routine part of the study of these cases.—Ed.)

OBSERVATIONS ON VAGINAL ABSORPTION OF PENICILLIN

S. Abel, C. J. Farmer and Jeanne Doucette

Northwestern University Medical School, Chicago, Ill.

Suppositories containing penicillin were inserted vaginally in patients with vaginitis, in patients free from vaginal pathology, and in a group of normal, young hospital nurses.   Blood level studies of penicillin were done in all groups.

From this study it is concluded that the degree of absorption and the resulting penicillin blood level are subject to great variation and are difficult to predict in any given case.   Apparently there is less absorption of penicillin from the normal vaginal mucosa than from the inflamed mucous membrane in a patient with vaginitis.

Because of the incidence of side reactions and, because of the unpredictable blood levels obtained subsequent to the use of penicillin vaginal suppositories, it does not seem rational to advocate this route of administration in preference to intramuscular injection or oral therapy when the desired result is the production and maintenance of a therapeutic blood penicillin level.

The real value of penicillin vaginal suppositories is in the treatment of vag-

initis where the local concentration of penicillin is of prime importance and the production of blood levels is only a matter of secondary interest.   1 figure.

(These studies are of interest, although the results suggest a lower degree andg reater inconstancy of absorbability of penicillin through the vagina than has been reported by Rock, Barker and Bacon (Science, 105: 13, 1947) and one or two other groups. Thus far it would seem that the intramuscular route is still the best for most indications. The use of penicillin suppositories for trichomonas vaginalis is being tried in various clinics, but my own limited experience with the method has not thus far impressed me with its effective-ness.—Ed.)

THE RECTOGENITAL SEPTUM

E. Uhlenhuth, W. M. Wolfe, E. M. Smith and E. B. Middleton

University of Maryland Medical School, Baltimore, Maryland

Surg., Gynec. & Obst., 86: 148–163, 1948

The authors have found that, with few exceptions, the rectogenital septum can be clearly demonstrated in the adult pelvis of both men and women. It represents most often a firm transverse membranous partition between rectum and urogenital organs, attached cranially to the peritoneum of the pouch and caudally to the urogenital organs. Usually, the septum can be demonstrated as an individual structure additional to, and independent of, the fascial capsules of the adjacent viscera.   However, there is a constant difference in relation of the septum to the capsules of the rectum and urogenital organs. From the capsule of the rectum the septum is separated by ample yet easily broken down areolar tissue, but adheres closely to the capsules of urogenital organs in the male and to the capsule of the vagina in the female.

From sagittal view, the rectogenital septum is continued without any visible boundary into the peritoneum of the rectogenital pouch. Its surface is glisten-ing, evenly membranous, of firm texture and sometimes of faintly greenish color. The peritoneum of the pouch, when inspected on its inner surface, presents along the line along which the septum is attached to its outside. The attach-ment of the septum is marked by a simple whitish line resembling a scar which may be slightly grooved. Sometimes slight wrinkles running perpendicular to this line may be seen in the peritoneum on either side. In extreme cases the peritoneum is thrown into marked folds perpendicular to the line and strong peritoneal cords are developed bridging across the line, evidently as safeguards against splitting the septum and reopening the fused part of the pouch. The obvious interpretation of these features is that the white, scar-like line on the inner surface of the peritoneum of the pouch is the line along which the dorsal and ventral walls of the pouch have fused with one another and that in some cases special structures have developed to prevent a reopening of the closed portion

of the pouch. In accordance with these views is the fact that application of cautious pressure along the white line will easily split the septum into its original dorsal and ventral halves.

With exception of one female full term infant in which the rectovaginal pouch still extended down to the pelvic floor, in 36 male and female infants varying from 6 months' intrauterine age to full term, the rectogenital pouch of the peritoneal cavity had already started to retract from out of the rectogenital space and the rectogenital septum was developed. As in adults, the rectogenital septum of infants is clearly differentiated as an individual membranous structure.

Relative to the prostate and to the vagina in the infant, the rectogenital pouch descends to a more caudal level than in adults; therefore, larger portions of prostate and vagina are covered by the peritoneum of ventral wall of pouch in infants than in adults. The extent to which the prostate and vagina are covered by peritoneum diminishes distinctly during the last months of intrauterine life, indicating that further retraction of the pouch takes place during this period.

By application of slight pressure to the bottom of the rectovaginal pouch in infants, one easily splits the septum into a dorsal and ventral leaf, corresponding to the dorsal and ventral walls of the pouch, through fusion of which with one another the septum has formed during earlier stages of development.

The writers conclude, from the evidence presented in this paper, that the rectogenital. septum, as shown from the first time by Cuneo and Veau, is of peritoneal origin and the result of fusion of the dorsal with the ventral wall of the rectogenital pouch. 14 figures.

(There appears to have been a resurgence of interest in the study of the anatomy of the pelvic structures during recent years, and this is all to the good. Some of these have confirmed older observations, but others have changed our ideas very materially. For example, the recent work of Huffman on the paraurethral glands has completely changed our concept of these structures (see abstract in June Survey). The study of the rectovaginal septum abstracted above is a worthwhile contribution, especially since the senior author is a highly trained anatomist of many years' experience.—Ed.)

MESODERMAL MIXED TUMOR OF THE VAGINA: REPORT OF CASE

G. H. MURPHY AND J. W. DuSHANE

Mayo Clinic

Proc. Staff Meet., Mayo Clin., **23**: 22–24, 1948

The first case of mesodermal mixed tumor of the vagina to be diagnosed at this Clinic is reported. The patient was a 33-month-old white child who, 7 months previously, had had a "botryoid sarcoma (rhabdomyoma) of the vagina" excised. Radium and roentgen therapy had been given to the operative site, but

several months later more vaginal bleeding had occurred. On the present admission, examination revealed a soft mass in the vagina. At operation the tumor was found to originate over a 5 by 2 cm. area on the right anterior vaginal wall. Frozen sections showed evidence of a high-grade malignant process and, since the tumor infiltrated the vaginal wall, a local removal only was performed. The child was discharged in good condition, but the parents were told that the prognosis was extremely grave.

Pathologic examination revealed a mesodermal mixed tumor of the vagina. The tumor consisted mostly of a myxomatous-appearing network formed by star and spindle-shaped cells and their processes. Other areas showed mitotic figures and giant cells. Young, striated muscle cells were present, and scattered among these were embryonic myoblasts. Some areas of the tumor contained a considerable amount of collagen.

Mesodermal mixed tumors are monodermic in origin and are found in the uterine body, cervix and vagina. The literature contains a wide variation of figures as to the incidence of mesodermal mixed tumors, undoubtedly due to the differing criteria of diagnosis. The vagina would seem to be the most common of the sites. Vaginal mesodermal mixed tumors have all occurred in very young females.

The prognosis in all 3 types is bad, the over-all mortality rate having been given as 95 per cent, and only one 5-year and one 10-year cure having been reported.

(As the authors state, these mesodermal mixed tumors may occur in either the uterus, the cervix or the upper vagina. Perhaps the best known variety is the so-called sarcoma botryoides arising in either the cervix or the vaginal vault. The fact that the teratomatous elements are always mesodermal is difficult to explain except on the hypothesis that mesodermal elements are, in early embryonic development, pulled down into the müllerian segment from the purely mesodermal Wolffian area, and this hypothesis, as a matter of fact, is the one which is most widely held as to the histogenesis of such rare tumors. The mesodermal element which seems to be most often found, though sometimes absent, is striated muscle, often of embryonic type, and apt to be overlooked unless carefully searched for. —Ed.)

TREATMENT OF CONDYLOMATA ACUMINATA WITH PODOPHYLLOTOXIN

M. Sullivan, M. Friedman and J. T. Hearin

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Podophyllin is a mixture of 4 components: podophyllotoxin, podophylloresin, picropodophyllin and quercetin. Forty-four patients with condylomata acuminata were treated with podophyllotoxin, with a percentage of cures of 81.5.

The percentage of cures with podophyllotoxin is comparable to that which the writers are obtaining with podophyllin. It is concluded that podophyllotoxin is the component of podophyllin responsible for its curative effect upon condylomata acuminata.

(The podophyllin treatment of condylomata acuminata, although introduced only a few years ago, has already established itself as an efficacious one, and, according to the authors' paper, the same can be said concerning podophyllotoxin, which they think is the active component of podophyllin. Whether or not it is to be preferred to the latter will no doubt soon be indicated by further experience with both.—Ed.)

THE UTERUS

HISTOLOGIC APPEARANCE OF COILED ARTERIOLES IN THE ENDOMETRIUM OF RHESUS MONKEY, BABOON, CHIMPANZEE, AND GIBBON

I. H. Kaiser

Carnegie Institution of Washington, Baltimore, Md.

The coiled arterioles of the endometrium of the rhesus monkey undergo a series of characteristic alterations during the menstrual cycle. At the time of ovulation, the arteriole fields are in the deep third of the endometrium, and the loops made by arterioles are 6 to 8 in number, while the arteriole wall is thin. In the progestational phase the loops increase in number, the fields become more superficial, and the vessel walls widen and acquire a swollen appearance. At the onset of ovulatory menstruation there are 20 or more loops in the field which is now in the superficial half of the endometrium. These changes recede after the onset of menstruation, and the postmenstrual vessel is simple and thin walled. In anovulatory menstruation, however, the fields are in the deep half of the endometrium, and include about 12 to 15 loops of relatively thin walled vessels.

Coiled arterioles are found in the endometrium of the baboon, chimpanzee and gibbon.

The concept that menstruation occurs because of ischemia produced by complexity of the coiled arterioles is untenable in view of these observations.

(This is a valuable study, but one which for the present adds considerable confusion to our ideas concerning the vascular mechanism of menstruation. The classical anatomical studies of Daron, with later the corroboration of Okkels and Engle, as well as the equally classical studies of Markee upon the behavior of the coiled arterioles of the endometrium, added a brilliant new chapter of our knowledge of the menstrual mechanism, especially as regards the actual bleeding phase. And now we have this study by Kaiser showing that the endometrial ischemia is not responsible for menstrual bleeding, so that Markee's explanation of this phenomenon will have to be re-evaluated, especially as the studies of Kaiser have indicated that in some species of the monkey family menstrual bleeding can occur from an endometrium in which there are no coiled artierioles at all.—Ed.)

CERVICAL CYTOLOGY IN DIAGNOSIS OF EARLY CANCER

J. E. AYRE

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The early diagnosis of cervical cancer is always a microscopic technic, involving a preclinical entity.   Such evidence argues for a total hysterectomy if hysterectomy is being considered.   It indicates more extensive treatment of cervicitis and erosion by electrocervical methods.   The widespread use of cytology should increase the percentage of surgical cures.

The evidence argues for the advantage of an annual cytologic test by a selective method to detect early carcinoma.   If, as the evidence indicates, early cervical cancer is a microscopic disease, single biopsies, or even multiple biopsies which depend on visual demonstration for localization of site, may fail to detect the focus of the growth.

To date, the writer has picked out a large series of women (about 115) who show cells suggestive of carinomatous tendencies using the spatula; yet in a surprisingly large number of these, single biopsies failed to detect any carcinoma.   Those cases, however, which did have a complete conization and serial sections of the entire squamocolumnar junction of the cervix, yielded 36 preinvasive carcinomas and a still larger number of studies showing cells exhibiting the structure of cancer without a lesion large or definite enough to be labeled preinvasive carcinoma.

The various cytologic methods of diagnosis include the vaginal smear, the endocervical smear, the endometrial smear, smear from the cervical external os, the selective scraping method and the cervical biopsy.   The writer believes that the selective scraping method, whereby scraping the circumference of the squamocolumnar junction of the cervix yields a true "surface biopsy" of the cells prior to their exfoliation, is the method of choice for identification of early microscopic squamous cancer of the cervix.   Vaginal and cervical smears will detect an abundance of cells in the presence of a "full blown" cancer.   Since squamous cancer of the cervix makes up 80 to 90 per cent of uterine cancer, routine methods of practice should be concentrated on early detection of this common offender. The greater sensitivity of the selective scraping method over other cytologic technics is suggested by the author's results with 15 early cervical cancers which were diagnosed using the spatula, while vaginal smears taken at the same time failed to show the cells.

Many of the cases showing only fragmentary evidence of growth have been cases in which there was chronic cervicitis, and study of the nuclear changes in the cases of chronic cervicitis does give the impression that inflammation bears some relation to malignant growths in this organ.   It is the author's belief, however, that other factors are necessary to produce morphologic changes of a malignant character in the cells.

Until a real cure for cancer is found, a yearly cytologic test offers the next best thing in diagnosis and control of uterine cancer. 1 figure.

(See comment on following abstract of paper by Wilcoxon and Falls.—Ed.)

AN EXPERIMENT WITH UTERINE CERVICAL SMEARS IN THE DIAGNOSIS OF GENITAL MALIGNANCIES

G. M. WILCOXON AND F. H. FALLS

University of Illinois School of Medicine, Chicago, Illinois

Ohio State M. J., **44:** 165–167, 1948

In this study the technique of vaginal smears was applied to the uterine cervix. After insertion of a vaginal speculum, the cervical os was exposed. Using a glass pipette attached to a rubber suction bulb, the bulb was compressed and the pipette inserted into the cervical canal for about one inch. Compression on the bulb was released and the pipette gradually withdrawn so as to collect the cervical mucous plug in the pipette. The slides were stained after the method developed by Papanicolaou.

Using this method, 236 cases were studied and followed in the hospital and clinic. Of the 236 patients 198 showed no evidence of cancer. Of the entire series 74.7 per cent had proved pathological diagnosis. In the series of 198 negative cases 18 mistaken positive diagnoses were made. This represents an error of 9 per cent in negative called positive cases. Of the total number of cases followed, these 18 mistakes represent an error of 7.6 per cent.

In the entire series of 236 cases, 38 were shown to have cancer. Of the 38 cancer cases 2 were called negative and are regarded as mistakes. One of the mistakes was a case of epidermoid carcinoma of the cervix which was called negative on the first reading. On a subsequent reading of the slide, malignant cells were found. The second case listed as a mistake was a leiomyosarcoma of the uterus from a degenerating fibroid. The uterine mucosa was normal and this malignancy probably never exfoliated any malignant cells into the uterine canal. These 2 mistakes in the 38 cases of malignancy represent an error of 5.2 per cent. In the series of 236 cases they represent an error of 0.84 per cent.

The positive cases included 21 cases of carcinoma of the cervix. Epidermoid carcinomas accounted for 18 of the cervical malignancies; the remaining 3 cases were squamous cell carcinomas. From the fundus, 7 cases of malignancy were demonstrated. Of these, 4 were adenocarcinomas, one was an adenoacanthoma and 2 were leiomyosarcomas.

The writers conclude that the cervical smear is an accurate method to be used in the diagnosis of female genital tract malignancies. A mechanical stage should be used routinely in examining all cervical smears. Criteria by Papanicolaou

and Meigs for the examination of vaginal smears can be used for the reading of smears prepared from the cervical os.   The results of a study of unknown cells in cervical smears correlated with surgical procedures and proved pathology are presented.

(While the authors conclude that the cervical smear is an accurate method in the diagnosis of cancer, it will be noted that they encountered 18 false positive diagnoses in 198 negative cases.   I feel sure that they would agree that the method is to be looked upon as of only supplementary value, and not comparable in decisiveness to properly performed biopsy, especially in the presence of a suspicious lesion.   In evaluating reports on vaginal smears, it must not be forgotten that the positive smears reported by many authors include many cases in which the smear is made simply as a supplementary procedure in cases of very frank cancer, in which the smear is certainly not necessary to establish the diagnosis. I presume that this applies to the present series, in which 74.7 per cent are said to have had proved pathological diagnoses.

These comments are not meant to reflect on the use of the vaginal smear method in all clinics where trustworthy cytologists are available to interpret them.   As I have repeatedly commented in these pages, the ideal application of the smear method is as a screening process in women with no bleeding and no grossly demonstrable cervical lesion, so that its most fruitful field would seem to be in cancer detection clinics, dealing chiefly as they do with ostensibly normal women.   Positive smears in such cases are not decisive, but they clearly point the way to further intensive study.   In the presence of a suspicious lesion of the cervix, I would personally prefer to do a biopsy, though there is certainly no reason why vaginal smears should not also be done for their correlative interest if these can be authoritatively interpreted.

I have also previously alluded to the procedure of surface curetting, either with a scalpel or a long-handled spoon with cutting edges, of the entire epithelium surrounding the area of the junction of the 2 types of cervical epithelium.   This paring process yields long strips of surface epithelium, allowing of far more comprehensive study than can be obtained by smears, as the whole thickness of the surface epithelium is obtained.   I have been doing this as a routine in all vaginal operations.   Only a slightly oozing surface is left, and this soon epithelializes.   This procedure seems to me to be better than the light scraping of a film of epithelial cells with the wooden spatula recommended by Ayre, with the preparation of a smear from the tissue thus obtained.   The strips which we obtain by our method are at once fixed in alcohol and ether, followed by centrifugalization, the tissue being then run through according to the ordinary paraffin technic.   Hematoxylin-eosin staining gives excellent results, and I do not think that many cases of early or preinvasive carcinoma will be missed by this method.   It is of course not a new principle, having been suggested by Schiller and others many years ago, but it appears to have been lost sight of in the more recent enthusiasm for the smear method.—Ed.)

AN EVALUATION OF THE VAGINAL SMEAR METHOD FOR THE DIAGNOSIS OF UTERINE CANCER

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Vaginal smears for cytologic study were collected on 500 consecutive patients admitted to the gynecologic ward of this hospital. The vaginal smears were read by numbers and later compared with the pathological and clinical findings.

Sixty-three patients had proved uterine carcinomas; 57 were squamous-cell carcinomas of the cervix, 5 were adenocarcinomas of the endometrium, and there was one fibrosarcoma. The vaginal smear findings afforded correct correlation in 474, or 94.8 per cent of the 500 patients, 44 being correct positives and 430 correct negatives. Incorrect results were obtained in 26, or 5.2 per cent of cases, 7 being false positives and 19 being false negatives.

In the 63 cancer patients, correct positive smears were obtained in 44, or 70.0 per cent. Negative smears were obtained in 19, or 30.0 per cent. In the 57 cases of cervical cancer, 17, or 28.8 per cent, were missed, while in the 6 patients with fundal cancer 2, or 33.3 per cent, were not detected.

Excellent correlation was obtained in the 437 patients who did not have carcinomas, correct negative smears being obtained in 430, or 98.4 per cent, while false positives occurred in only 7, or 1.6 per cent. It is emphasized that the good over-all correlation of 94.8 per cent was largely influenced by the high proportion of negative patients, and the authors point out that this factor has influenced the results in some of the earlier studies by other workers.

The factors influencing the accuracy of the cytologic method for the diagnosis of uterine cancer are discussed. It is suggested that smears taken from the vagina and cervix are preferable to those from either source alone. The advantages of repeated samplings are emphasized by the high percentage of missed positive cases in the present study, in which single samplings were used. Finally, the influence of the personal factor in the interpretation of atypical slides is pointed out. Much can be said on both sides of this question. If the diagnostic criteria are too rigid it is possible that positive cases will be overlooked. However, if smears are reported positive on an insecure basis, unnecessary biopsies or even operations may be performed. Even with rigid standards, the authors have had instances in which biopsy or operation failed to reveal a malignant lesion; yet these have been more than compensated for in several cases in which operation was performed on the basis of a vaginal smear alone and carcinoma found. One such case proved to be a myosarcoma of the tube.

The value of the vaginal smear as a routine procedure on the gynecologic service is indicated not only as a diagnostic aid in the detection of uterine cancer but in affording information concerning the functional status of the patient and infections of the genital tract. The necessity for recognizing the limitations of

the cytologic method is emphasized, since its indiscriminate use may lead to failure in employing more absolute methods of diagnosis or indiscriminate surgery.

(See comment on following abstract of paper by Posey and Cunningham.—Ed.)

IMPRESSIONS OF THE VAGINAL SMEAR TECHNIC IN THE DIAGNOSIS OF CERVICAL CANCER

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A summary is presented of the results of examination of 3,808 vaginal smears from 1,435 patients. Repeat smears were examined from 20 patients. The smear diagnoses were: positive (cancer cells present), 13 cases; doubtful (equivocal anisonucleosis present), 41 cases; negative (no atypical cells present), 1,381 cases.

Biopsy material showed cancer in 4 of the cases reported negative by smear examination. Two of these false negatives were cases of carcinoma of the uterine fundus and are not discussed here. One of the remaining 2 false negatives was a case of carcinoma *in situ* verified by 3 biopsy specimens. The remaining false negative was from Grade III squamous cell carcinoma of the cervix; the smears from this patient were too thin for proper evaluation.

Proof of the presence of cervical carcinoma was revealed in 9 of the 13 reported positive cases. Two of the 4 remaining patients are not available for follow-up. A third was found negative on a new set of smears, and the changes present were believed to be those of menopause with anisonucleosis due to low estrogen. The fourth patient whose primary smears were reported positive had had radiation treatment for cervical cancer 8 years before. Biopsy 5 and 6 months before the smears were made revealed no evidence of residual cancer. Physical examination reveals no evidence of recurrence. It was felt that the changes were those of low estrogen and probably were not suggestive of neoplasia.

Of the 41 cases reported doubtful, 24 can be eliminated as negative on the basis of biopsies, repeat smears and re-evaluation of original smears. Another case proved to be an adenoma malignum of the fundus. Sixteen of the doubtful positives await further study. Confusion has been greatest in smears from patients with low estrogen levels plus infection.

In discussing these results, the authors state that the most practical criteria for recognizing cancer cells in the smears were cellular pleomorphism and basophilia. Both of these alterations in cytology are a function of the rate of cell growth, and in slowly growing tumors the changes may be too minimal to recognize.

The rate of desquamation of tumor cells is a function of surface area and rate of growth. Experience has shown that cancers with small surface areas and of slow rate of growth are diagnosed with difficulty.

· The dilution of tumor cells is a function of the rate of desquamation and the amount of diluent. In acutely infected cervices the exudate is large in volume and highly cytotoxic.

It is concluded that the smear method in selected cases gives a better sample than the biopsy and is a very useful adjunct. This is particularly true in endo-cervical cancer. The smear method is technically simple but requires excessive examining time and skilled interpretation. Justification of the smear method as a screen test is yet to be established. 5 figures.

(This paper is a bit more conservative than are some of the overly enthusiastic ones which have appeared in advocacy of the vaginal smear method, with too little concern for the pitfalls of the method, especially in the hands of insufficiently trained cytologists. There is no question that many such are now employing it without due regard to its limitations. Here are two men, whose report of nearly 4000 smears indicates that they have had a great opportunity to perfect themselves in the technic, and who state that "justification of the smear method as a screen test is yet to be established." And it is as a screen test that the method appears to have achieved an established place. Even the most highly trained cytologists have made no claims as to its decisive diagnostic value as compared to biopsy, in spite of certain limitations of the latter.

In my comment on the papers of Ayre and Wilcoxon and Falls in this issue, I have called attention to the fact that thorough surface scraping of the cervical squamous epithelium in the zone of predilection for cancer would seem to remove the most important limitation of biopsy encountered in those cases where there is no visible lesion of the cervix.

Everyone is agreed as to the supplementary value of vaginal cytological studies in the diagnosis of cervical cancer, but we should not lose sight of the woods for the trees.

The paper of Scheffey, Rakoff and Hoffman likewise stresses the limitations of the cytologic method and warns that its indiscriminate use may lead to neglect of more absolute diagnostic methods and, what has not yet been sufficiently emphasized, to indiscriminate surgery. There are, of course, no statistical data on this point, but nothing is more certain than that a good many unwarranted operations have already been done because of the findings in smears which were done by insufficiently trained cytologists or misinterpreted by even well trained men. None of these things is a criticism of the vaginal smear method in the hands of those who appreciate that it is, as I believe it should be, only an adjunct to more decisive methods of diagnosis, and that it is not by any means a sine qua non in the study of all cases.—Ed.)

THE EARLY DIAGNOSIS OF CARCINOMA OF THE CERVIX AND OF THE CORPUS UTERI

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The effectiveness of the present day methods of treatment of carcinoma of the uterus depends upon an early diagnosis. The early detection of cancer should

be most easily attained in those areas of the body which can easily be visualized and examined. Cervical cancer is available to direct inspection by the physician, and the percentage of cures in cancer of the cervix should be high, although the over-all percentage of 5-year cures is about 37.5 per cent. Many of the failures are due to negligence of the patient in consulting a physician, but unfortunately many other failures are directly due to the physician who fails to make a proper examination. The only 2 early symptoms are vaginal leukorrhea and irregular vaginal bleeding. The early detection of cervical carcinoma depends primarily upon pathologic examination of the cervix or its desquamated epithelial cells.

Carcinoma of the endometrium also has only 2 early symptoms; a watery vaginal discharge and irregular vaginal bleeding. A thorough and carefully performed diagnostic curettage should be done and the curettings examined microscopically. Since fibromyoma uteri and endometrial carcinoma frequently occur in the same uterus, a surgeon contemplating hysterectomy upon a woman near the menopausal age should precede the major operation by diagnostic curettage. If carcinoma of the endometrium is found, then the operation should be a panhysterectomy.

(While preliminary curettage is often advisable before hysterectomy for myoma, there are frequent cases in which I do not believe its omission is culpable. However, when it is not done, the uterus should be opened immediately after removal. Should there be any suspicion of malignancy of the endometrium, it is much better to find this out when the abdomen is open and something can be done about it than to get the disturbing report of cancer a day or two after a conservative operation is done. For similar reasons it is well to cut into myomatous tumors before the abdomen is closed, as in at least some cases the gross appearance justifies the suspicion of sarcomatous change.—Ed.)

A COMPARISON OF THE ACCURACY IN DIAGNOSIS OF THE VAGINAL SMEAR AND THE BIOPSY IN CARCINOMA OF THE CERVIX

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Since 1942, 181 cases of epidermoid carcinoma of the cervix have been examined by both vaginal smear and biopsy. In 148 of these or 82 per cent, both the first vaginal smear and first cervical biopsy were positive for cancer. There were 16 false negative biopsies and 14 false negative smears; in addition to these there were 3 cases in which both methods failed. There were in all 19 cases, or 10.5

per cent, in which the first biopsy was negative. Errors in biopsy diagnosis are based on first, the right area was not chosen for biopsy, second, misinterpretation of the specimen and third, insufficient tissue for diagnosis. Of the 181 cases, there were 17, or 9.4 per cent, in which the first vaginal smear was reported negative. Failure of the vaginal smear method is attributed to first, occasionally a tumor will not desquamate cells into the vagina; second, the cancer cells may not have been seen at the first examination, third, malignant cells may be misinterpreted as benign. Although the first biopsy report was negative in 10 per cent of the cases and the first vaginal smear negative in 9 per cent, there was only 1.7 per cent error in initial diagnosis when both methods were used. It is of particular importance to note which method proved to be the more reliable in diagnosing early lesions. There were a total of 16 cases of cancer in situ in 181 cases under study. The first biopsy failed to make a positive diagnosis in 8 of these, but the first smear was positive to cancer in 14 of the same 16 cases. From this study the authors conclude: 1. that the vaginal smear is diagnostically as reliable as the biopsy taken in a large general hospital; 2. that an extremely high percentage of cases can be diagnosed accurately if the 2 methods are used together, and finally that the vaginal smear is of especial value in the diagnosis of the very early malignant lesions of the cervix.

(The authors are among the leading advocates of the vaginal smear method in the diagnosis of uterine cancer, and they make out a good case for it in the study of the present group of cases. They obviously do not recommend dependence upon it alone, and this, it seems to me, would be absurd in the presence of a suspicious lesion which invites the more decisive biopsy. This, after all, is the problem which faces the average practising gynecologist, and it is quite different from that which is involved in the examination of ostensibly normal women, with no cervical lesion of any kind and no bleeding whatsoever. It is this latter group of patients who are especially numerous in cancer detection clinics.

In women with perfectly "clean" cervices, the usual type of biopsy, with scalpel or biopsy clamp, is a pretty random procedure, even if done at various points, for even then one could easily miss an extremely early or preinvasive lesion. But the vaginal smear is not the only alternative in such cases. Thorough surface scraping of the cervix in the region of the junction of the squamous and cylindrical epithelia, the usual seat of carcinoma, is, in my judgment, more likely to reveal microscopic evidence of early lesions than the vaginal smear, as the cancer cells can be expected to occur in only highly attenuated form in the vaginal pool. The surface curetting, however, yields long strips of epithelium, and the difficulties of microscopic diagnosis are far less than those involved in the recognition of individual cancer cells among all the varied elements of the vaginal smear.

I believe that this plan of surface scrapings was suggested by Schiller in one of his early papers on preinvasive cancer, something like 20 years ago, but it is only in the past year or two that it has been seriously applied by a number of workers, such as Ayre and Hunter. I have employed it throughout the past year and almost routinely in cases in which any vaginal procedure is carried out. The perfect instrument for the scraping has not yet been devised. Ayre recommends a thin wooden spatula, but an ordinary scalpel seems to me better for most cases. The scraping leaves only a very slightly oozing surface, but this epithelializes very quickly.

While the fine scrapings can be fixed and stained like a vaginal smear, we have gotten better results, after washing the knife blade off at once in the alcohol-ether fixative, by centrifugalizing the latter and then running the tiny bits of tissue through the usual paraffin technique, with hematoxylin-eosin staining. If some sort of tiny paring instrument, similar

to the dermatome employed by plastic surgeons in the preparation of grafts, could be devised in a form adaptable to the cervix, it would be quite ideal.

The study of such cervical scrapings will be of great value also in throwing light on the hormonal responses of the cervical squamous epithelium. For example, it has always seemed to me that hormonal factors may well explain some, perhaps many, of the milder cases of so-called "basal cell hyperactivity," which is somewhat prematurely being spoken of by some as a possible precursor of cancer. We are planning a study of our cervical scrapings from this point of view when a sufficiently large amount of material has been accumulated.

It is probably easy to see that I am a bit of a reactionary as far as vaginal cytology is concerned, and not at all convinced that it will achieve great practical value in the future except as a screening method, always to be checked with some type of biposy. I am heartily in favor of any procedure which will intensify our search for very early cancer, and I believe that vaginal cytology should be one of the diagnostic measures employed in all cancer detection clinics. Moreover, I believe it would be a good plan to try to develop trained cytologists in all large clinics, if for no other reason than to explore the possibilities of the method.

On the other hand, I feel very strongly that there are only a handful of cytologists now fully qualified in this field, and that it is being employed by a larger number who are not sufficiently expert, and that its limitations and difficulties are not always appreciated. It would seem wise that those interested in the problem continue their work earnestly and quietly until the method can be better evaluated from the standpoint of practical applicability. The method seems to me to have been a bit over publicized, even in the lay press, so that there are patients, and even gynecologists also, who may feel that vaginal smear studies should be an essential part of the examination of every cancer case. I believe that this is a wrong viewpoint.—Ed.)

ANAPLASTIC CERVICAL EPITHELIUM; RELATIONSHIP TO CERVICAL CARCINOMA

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Because of the tremendous importance of recognizing cervical cancer in its earliest stage, material bearing on non-invasive carcinoma was analyzed to ascertain the relationship between atypical non-invasive and invasive lesions. Of 1,815 cervical tissues obtained by biopsy and hysterectomy, 16 showed non-invasive anaplastic epithelium, 6 early invasive and 293 frankly invasive carcinoma. The remaining 1,500 specimens were benign.

The principal cellular changes observed in anaplastic cervical epithelium were nuclear hypertrophy, hyperchromatism, and variation in size and shape of the nuclei. The basement membrane, although remaining intact, was often disordered in contour, producing a lobulated effect. It was also found that the epithelium failed to differentiate as readily as normal. This impairment of differentiation is important in distinguishing non-invasive carcinoma from hyper-

plastic and metastatic growths in the cervical epithelium. Histologically, with the exception of invasion, the anaplastic epithelium was indistinguishable from invasive carcinoma.

The authors found, by nuclear measurements, that the relative nuclear volume curves were similar for anaplastic and carcinomatous epithelium. Both of these differed strikingly from the normal. On the basis of data presented, the writers suggest that in anasplastic as well as in carcinomatous epithelium, polyploidy and polyteny account for the hypertrophy, hyperchromatism and variation in size of nuclei.

Four lines of evidence are presented which are felt to point to the malignant nature of anaplastic cervical epithelium. (1) The foregoing analysis demonstrates the fundamental histologic identity of the cells of noninvasive to those of invasive carcinoma. (2) The simultaneous occurrence in a cervix of epithelium bearing characteristics of anaplasia in one area but not invading, and of invasive carcinoma in another area, would strongly speak for a continuity of the 2 processes. (3) A number of investigators have shown by clinical study that patients with anaplastic cervical epithelium may eventually develop invasive carcinoma of the cervix. (4) It has been shown in the pathogenesis of experimental tumors that abnormal growth passes through several stages. It is believed that there is an analogy between the demonstrated stages in experimental carcinogenesis, and anaplastic noninvasive and invasive carcinoma of the human cervix. 3 figures.

(While pathologists are pretty well agreed on such criteria of cellular anaplastic activity as the authors enumerate, they must by now all appreciate the fact that the finding of such changes does not by any means always indicate clinical malignancy, or even histological malignancy in its full sense, including the demonstration of invasiveness. As a matter of fact there is still confusion as to the histologic criteria of invasiveness. With the full-blown picture of very frank cancer, the evidence for this is unquestioned, with not only an obvious break-through of the basement membrane, but also such unquestioned evidences of lymphatic permeation as cancer cell emboli in the lymphatic vessels.

But in the very early and precursory lesions now being studied so extensively and intensively, pathologists will often differ as to whether the basement membrane, when perhaps only a bit hazy and irregular, is actually broken through. Again, there are many cases of preinvasive carcinoma in which wide buds project downward from the surface, which appears to have buckled as a result of the greatly increased activity and thickness of the basal layers. And yet these buds present a sharp and clear basement layer.

Again, often this downward budding of the deeper layers extends along the framework of the glands, much as in the base of benign epidermidization. Are such changes adequate evidence of invasiveness? Probably not, and yet many pathologists seem to accept them. When real penetration is not present in one section, it may be revealed by the study of a great many more, so that the proper evaluation of such lesions imposes an enormous amount of work upon both technicians and pathologists, more than is feasible in many laboratories.

The real significance of such histological changes could probably be solved within a few years if we could use the human animal as a guinea pig, and let such early, doubtful lesions unfold their careers and thus see whether they develop into frank cancers. But the gynecologist must protect the life of his patients and such lesions are likely to be removed by some such conservative plan as excision, conization, cervical amputation if they are thought to be only preinvasive, or by hysterectomy or radiotherapy if the suspicion of malignant potentiality is sufficiently great. Already our ideas as to the life history of cervical cancer

have undergone profound change, and even with the limitations imposed by the prime con-sideration of the patient's welfare, the accumulating experience of the many clinicians and pathologists now interested in the study of these lesions will crystallize into more clearer concepts than are as yet possible.—Ed.)

CARCINOMA OF THE UTERUS. OVARY AND TUBE

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The preparation of this paper drew on an extensive experience covering 27 years and the observation of well over 3,000 patients with cancer of the female generative organs. The author states that the common habit of looking forward to a new cancer "cure" as the only solution to the problem of cancer control serves as pap for a defeatist philosophy. Unless the potentialities of a new "cure" are considerably greater than either surgery or radiation, the problem will remain as it is today, essentially one of prevention and early treatment. Most important is the fact that physicians now have within their grasp the means to exert a powerful influence on many cancers, and especially cancer of the female genitalia.

The uterine cervix is the commonest site for cancer of the female generative tract, constituting 65 per cent of all cancers of these organs. Regular periodic examination of the cervix plus correction of minor lesions and biopsy of all suspicious lesions followed by treatment in proved cases would reduce tremend-ously the mortality from this cause.

More than 90 per cent of cervical cancers are of the epidermoid or squamous cell variety, most of the remainder being adenocarcinomas. In its earliest stages the cancer is most commonly found at the junction of the squamous epithelium of the cervical canal; from here it spreads until the entire vaginal cervix is in-volved. Further spread occurs by extension into the parametrial tissues, broad and sacrouterine ligaments, bladder and vaginal mucosa. Extension also occurs by way of the lymphatics to the regional lymph nodes, and it is the cancer cells in the parametrial tissues and involved lymph nodes that present the greatest obstacle to cure. The chief and often the only symptom is spotting or bleeding; this is characterized by being: (a) intermenstrual or irregular; (b) progressive, increasing in frequency and amount; and (c) prone to follow trauma, such as postcoital spotting. About 15 per cent of patients complain only of a nonbloody leucorrhea, and some are symptom-free, emphasizing the need for periodic exam-ination.

Every case should be proved by taking tissue for histologic examination. In most instances biopsy of the cervix is an office procedure requiring no anesthesia

The clinical extent of the neoplastic growth is the most important single factor in determining prognosis. For practical purposes there are 4 categories: 1. Clinical group I includes very early proved lesions still confined to a small portion of the cervix. 2. Clinical group II includes more advanced cancers than in group I, but they are still confined to the cervix. Cancers in groups I and II present a favorable prognosis. 3. Clinical group III includes cancers with questionable extension beyond the cervix, in which it is difficult to decide whether or not there is parametrial extension. 4. Clinical group IV includes all advanced cases, whether they reveal extension into vaginal vault, parametrial invasion or remote metastasis. Evaluation of clinical extent demands visualization of the cervix through a speculum and careful rectal palpation of the parametrial areas. In histologic grade I the invading cells show considerable resemblance to the normal epithelium of the area involved. There is considerable differentiation. In grade III, the neoplastic cells are highly undifferentiated, having completely lost their resemblance to the normal cell type. Here is seen widespread infiltra-

TABLE 2

Survival rates for carcinoma of the cervix based on clinical extent at time of treatment
(University of Michigan)

CLINICAL GROUP	5 YEAR		10 YEAR		15 YEAR	
	Number	Percentage surviving	Number	Percentage surviving	Number	Percentage surviving
I	45	89	18	78	2	100
II	104	57	55	44	4	75
III	218	48	142	32	11	36
IV	669	36	317	12	14	0

tion of neoplastic cells with deep-staining nuclei of varying sizes and numerous mitotic figures, reflecting a high degree of malignancy. Histologic grade II is an intermediate phase. There may still be seen in some areas a resemblance to normal cell architecture, but this resemblance is only spotty or incomplete.

So much depends on the clinical stage of the disease when treatment is first instituted that it is best to discuss survival rates in relation to clinical grouping, as shown in table 2.

There are at present 2 acceptable methods of treatment for cancer of the cervix: irradiation by means of high voltage roentgen rays and radium, and radical surgical intervention. The writer only briefly mentions these methods, since he does not believe the actual treatment of cervical cancer falls within the domain of the general physician. By surgical intervention is meant radical hysterectomy of the Wertheim type, bilateral salpingo-oophorectomy and pelvic lymphadenectomy. This is confined to selected cases. This, definitely, is not an operation for the untrained or inexperienced. This also applies to treatment by radiation. Few physicians have the equipment or training for administering adequate radiation therapy. As previously stated, early diagnosis is the most important single

factor in reducing mortality and morbidity.   Early diagnosis is to a large extent the domain of the general practitioner.

Cancer of the endometrium constitutes about 15 per cent of all cancers of the female generative tract.   It occurs most frequently in postmenopausal women and is generally an adenocarcinoma.   Clinical grouping is generally based on size of the uterus, evidence of parametrial extension and uterine fixation.   The commonest symptom is spotting or bleeding.   About 25 per cent of patients have a semipurulent leucorrheal discharge, and about 5 per cent have no symptoms.

Diagnosis of endometrial carcinoma is based on histologic confirmation of tissue obtained by curettage.   Hospitalization and thorough scraping of the uterine cavity under anesthesia is most dependable.   Slight bleeding following bimanual examination of the uterus is suggestive.   In every instance of irregular spotting or bleeding in adult women, cancer must be suspected until proved otherwise.

The advanced case of endometrial carcinoma is treated by high voltage roentgen therapy in combination with a multiple capsule intrauterine application of radium.   High voltage and roentgen therapy or intracavitary radium therapy is also used in the management of early, more favorable cases, especially when the patient's general health does not warrant operation.   The preoperative use of irradiation followed in 6 to 8 weeks by complete extirpation of the uterus and adnexa in properly selected cases seems more logical and likely to contribute to greater permanence of cure.   Promptly recognized and properly treated endometrial carcinoma permits a good prognosis.

Ovarian carcinoma constitutes only 10 to 20 per cent of all cancers of the female generative organs.   Though much less common than cervical cancer, it presents a greater diagnostic and therapeutic problem.   It may occur in young women and children, but is primarily a disease of postmenopausal women.   The degree of malignancy may range from the rapidly growing teratoma to the commoner, more slowly growing papillary cystadenocarcinoma.   The characteristic "silence" of early ovarian cancer is another reason why periodic examination is imperative in the control of pelvic cancer.

The diagnosis of ovarian cancer is made on the basis of histologic analysis of tumor tissue taken at operation.   In every case of ovarian enlargement, especially of the solid variety, the possibility of ovarian neoplasia must be kept in mind.

In general, complete surgical removal of both ovaries, tubes and the uterus is indicated in histologically diagnosed operable cases of ovarian cancer.   Where frozen section facilities and the services of a pathologist are not immediately available at operation, a conservative attitude toward the healthy appearing ovary should be adopted.   If the removed neoplasm proves to be a cancer, a second laparotomy for removal of the remaining ovary, uterus and tubes is indicated.   A possible exception is the young woman in whom the removed ovary shows an extremely early lesion; such a patient must be closely observed.   Preoperative or postoperative roentgen therapy may be desirable in all but the extremely early lesions in young women in whom a normal ovary was left.

Primary neoplastic involvement of the fallopian tube is exceedingly rare, constituting only 0.1 per cent of the cancers seen in the Gynecology Tumor Conference. Most primary tube cancers are of the papillary adenocarcinoma variety. During early growth the lesion is likely to be asymptomatic or silent in development. Bimanual palpation may, however, reveal a firm enlargement which cannot be accounted for on the basis of infection. The presence of an abnormal bloody vaginal discharge has been reported in some cases.

Palpation of a firm or nodular movable tube may lead one to be suspicious, but it is unlikely that the diagnosis will be made without thorough investigation, as by cytologic study of a cervical smear, possibly visualization and biopsy through the cul-de-sac or at laparotomy. The treatment, if diagnosis is made in time, is preferably surgical extirpation of both tubes, ovaries and the uterus. High voltage roentgen therapy might prove helpful as a postoperative procedure and as a life-prolonging measure in the inoperable case.

The writer concludes with a general discussion on control and prevention of pelvic cancer. While no one knows enough about cancer to permit dogmatic statements, long and careful study has clearly demonstrated one thing about which there can no longer be the slightest doubt, namely, the tremendous value of prevention and early detection.

(The author of this paper has long been a student of uterine cancer and has published many valuable studies based on a very large clinical experience. The general review abstracted above, therefore, may be considered an authoritative one, expressing the best opinion of the day on the gynecological types of cancer. It should be of especial interest to general practitioners, to whom it is primarily directed, because the patient's fate is so often dependent upon the intelligence and alertness of the family physician.—Ed.)

MALIGNANT LESIONS OF THE UTERUS ASSOCIATED WITH ESTROGEN-PRODUCING OVARIAN TUMORS: REPORT OF TWO CASES

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The association of malignant lesions of the uterus with estrogen-producing neoplasms of the ovary has previously been noted and suggests the possible importance of the estrogens as carcinogenic agents in the human female. Two such cases are presented in this paper and may be summarized as follows:

Case 1.—A white woman, aged 64 years, complained of pain and fullness in the lower abdomen of 8 months' duration, and loss of 16 pounds in the last 6 months. Twenty-one years previously, roentgen therapy had been given for uterine fibroids, after which the patient had seemed well until the onset of vaginal bleed-

ing 6 years ago. Intrauterine radium temporarily controlled the bleeding, but there had been several bleeding episodes during the ensuing years. An ulcer had been present on the abdominal wall since administration of roentgen therapy 21 years earlier.

The entire lower abdomen was filled with a large, irregular, fixed mass. At laparotomy the omentum was a thickened solid mass adherent to the right lateral abdominal wall. A difficult total hysterectomy and bilateral salpingo-oophorectomy were performed and a large amount of omentum excised. The section of abdominal wall containing the ulcer was also removed.

The right ovary contained a granulosa cell tumor with areas of malignant change, grade 2. An adenocarcinoma, grade 2, was present in the fundus uteri. There were multiple fibromyomas, several containing leiomyosarcomatous changes of grade 3 malignancy. There was an implant of granulosa cell carcinoma on the posterior surface of the uterus. The omentum contained a metastatic granulosa cell carcinoma, grade 2. The segment of abdominal wall showed ulceration and an extensive basosquamous cell epithelioma, grade 3. The patient died 2 months after operation.

Case 2.—A white woman, aged 46 years, complained of bloody vaginal discharge and pain in the lower abdomen and back of about 2 weeks' duration. Six years previously, intrapelvic radium had been given to prevent further pregnancies and had been followed by amenorrhea for 2 years. For the past 6 months, profuse, almost daily vaginal bleeding had occurred, and the patient had lost 20 pounds during this time.

The vagina was nearly filled with a necrotic mass. The uterus was enlarged to the size of a 3 months' pregnancy; it was firm, movable and nontender.

The vaginal mass was cauterized and a pack inserted. The abdomen was then opened. The uterus was enlarged and freely movable; the left ovary was enlarged by a nodular yellowish tumor. Total hysterectomy and bilateral salpingo-oophorectomy were done.

The uterus contained a pedunculated necrotic sarcoma, grade 4, of the endometrial stroma. In addition, an endometrial adenocarcinoma, grade 3, and an adenomyoma were present. The left ovary was replaced by a solid, encapsulated theca cell tumor which showed areas of sarcoma, grade 1. The patient recovered.

This report brings to 15 the number of malignant lesions of the uterus which have been found in conjunction with the 87 estrogen-producing ovarian tumors observed at the Clinic. The incidence of malignant lesions of the uterus in the entire series is 17.2 per cent.

The writers discuss the suggestive, although not conclusive, evidence that uterine carcinoma may be produced by estrogens. Cervical carcinoma has been reported in mice receiving estrogens. Typical endometrial hyperplasia develops in animals as a result of stimulation with estrogens. In humans, hyperplasia of the endometrium is frequently found in association with carcinoma of the uterus and, in postmenopausal women, occurs nearly 5 times as frequently in the presence of malignant lesions as when none exists. Endometrial carcinoma

is rare in oophorectomized women. Menstruation after the age of 50 is seen 4 times as often in women with uterine carcinoma as in women without uterine carcinoma.

Ayre and Bauld studied 150 cases of proved malignant lesions of the uterus and found that the vaginal smears of the majority showed evidence of high activity of endogenous estrogen. Of 20 additional patients, 90 per cent were found to have, in addition to the increased amount of estrogen, an average excretion of thiamine of less than half the amount which was average for a group of controls with normal estrogen levels. Previous observations suggested that deficiency of the B complex vitamins, particularly thiamine, may result in subclinical diminution of hepatic function sufficient to retard metabolism of estrogens.

The only report of proved malignant disease of the uterus following prolonged estrogen administration is that of Fremont-Smith and his associates, whose patient, from the age of 43 to 51 years, received a total of more than 11,500,000 rat units of estrogenic substances with only one short interruption. In the fifth year of treatment, an endometrial biopsy showed endometrial hyperplasia. Vaginal staining occurred 2 years later, with vaginal bleeding the following year. The excised uterus showed adenocarcinoma.

The authors mention briefly 2 possible etiologic factors other than estrogens, i.e., fibromyomas and radiation.

Dockerty, in his discussion of this paper, states that among the 55 postmenopausal patients from the group of 87 functioning ovarian tumor cases seen at the Clinic, the incidence of associated uterine carcinoma was 27.3 per cent. This is 100 times as high as would be expected if the 2 lesions were merely coincidental.

Since it seems clear that granulosa cell tumors are dangerous both from the standpoint of themselves metastasizing and of producing associated endometrial malignancy, there are certain practical applications in surgical therapy. It would seem wise to be satisfied with local removal of the encapsulated granulosa cell or theca cell tumor in the young woman. However, when the tumor is poorly encapsulated or ruptured, or if the patient has reached the menopause, panhysterectomy seems the wisest choice, with postoperative treatment with roentgen rays reserved for those in whom there is the possibility or probability of peritoneal soiling by malignant cells. 2 figures.

(The fact that in one clinic, large as it is, 15 instances have occurred in which estrogen-producing ovarian tumors have been associated with endometrial carcinoma, an incidence of 17.2 per cent of the 87 ovarian tumors of this type, is very impressive, and it justifies the belief that the latter play an important role in the development of the uterine malignancy. I rather doubt that this figure of 17.2 per cent incidence would be approached in the experience of other clinics and laboratories, which brings up a very important point. The estrogen produced by this type of ovarian tumor, just like estrogen administered orally or hypodermically to the postmenopausal woman, produces varying degrees of proliferative activity in the endometrium, and not infrequently this hyperplastic effect assumes an atypical form, producing a close histological simulation of adenocarcinoma, and not infrequently leading to the incorrect diagnosis of malignancy. Such pictures have been described in 2 recent publications (Gusberg, S. B., Am. J. Obst. & Gynec., 54: 905, 1947 and Novak, E.

and Rutledge, F. Ibid, 55: 46, 1948). There is not the slightest doubt that at least some of the cases reported in the literature of endometrial carcinoma in association with granulosal or thecal ovarian tumors represent errors in pathologic diagnosis, as an examination of the published photomicrographs will reveal.

On the other hand, there is not the slightest question that in other cases genuine adenocarcinoma is present in the endometrium of such published cases. The moral is that no case of this sort should be published without adequate photomicrograhic illustrations. Again, authors should bear in mind that these estrogen-producing ovarian tumors may engender in the endometrium either a very frankly benign hyperplasia, a pseudo-malignant type of hyperplasia or a genuine adenocarcinoma. Unfortunately the distinction between the latter two is not always easy, as emphasized in both of the papers cited above, but in others it can be made with reasonable accuracy.

These comments are not made in any captious spirit, and are certainly not meant to reflect upon the pathologic acumen in the many excellent laboratories which have reported instances of this combination. They are intended only to call attention to a possible source of error. This is the day of Registries for all sorts of pathologic conditions. The particular subject under discussion is of course too small to warrant a Registry of its own, but it would probably be a good plan and in the interests of scientific accuracy for all of us encountering such cases to fortify ourselves with the composite opinion of a number of competent gynecological pathologists before placing our cases in the literature.

Since this combination of tumors is much more common in postmenopausal women, its occurrence naturally raises the question of whether the role of estrogen in the production of the uterine cancer is causal or predisposing. The latter is, on the basis of available evidence, the more probable of the two, in spite of the fact that in at least one laboratory animal, the mouse, it has been possible to produce cervical (not corporeal) cancer, by means of estrogens. As I have discussed in previous comments in the Survey, two factors appear, on the basis of all the scientific work which has been done in all fields, to be concerned in the production of cancer.

One of these is some unknown, innate, genotypic predisposition, in which heredity may be not unimportant. This is often so strongly developed that cancer is destined to break out somewhere, in the entire absence of any contributing factor, such as chronic irritation. Where the susceptibility is less marked, it requires this, plus some irritation to incite the cancer, and this irritation may be inflammatory, traumatic, chemical or hormonal (estrogenic). Finally, there are fortunate individuals with so little inborn susceptibility that no matter how great or constant the irritative stimulus, cancer will not develop. This summation, oversimplified though it is, fits in with the results thus far accepted in the field of cancer research.

The fact that postmenopausal estrogenic stimulation of the endometrium appears to be much more apt to be carcinogenic than during reproductive life is suggested by such studies as those of Taylor, Novak and Yui, and others. The fact that progesterone counteracts the tumorigenic effects of the estrogens in certain types of experimental cancer, and that this protective action of progesterone is of course lacking after the menopause, may not be without significance.—Ed.)

THE ROLE OF TRANSVAGINAL ROENTGENTHERAPY IN THE TREATMENT OF CARCINOMA OF THE CERVIX

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Surg., Gynec. & Obst., 86: 480–486, 1948

The author believes that transvaginal roentgen therapy is a valuable adjunct of the external pelvic irradiation in the treatment of carcinoma of the cervix, and that it is the treatment of choice of carcinomas of the cervical stump. The writer has designed a speculum that avoids irradiation of the introitus while permitting the expansion of the beam of rays through a shaft transparent to radiations. In its present form the use of this speculum results in the irradiation of a circular field that opens to 6 cm. in diameter at the level of the cervix; protection of the rectum or bladder is facilitated by removable metal aprons placed within the shaft of the speculum. For his work, the author uses a set of 3 specula with different diameters and removable shafts of 3 different lengths for each of these specula.

Following a course of external pelvic roentgen therapy, lasting approximately 6 weeks, patients receive the course of transvaginal irradiations without interval of rest. The largest and longest speculum that can be introduced is chosen. The beam of rays is directed toward the side of invasion when this is unilateral. In general, 10 consecutive treatments of 400 roentgens, or a total of 4,000 roentgens in 11 days, were given to the patients in this paper. All patients are given a course of external and internal irradiations.

From Feb., 1943 to June, 1944, 76 patients with carcinoma of the cervix, not previously treated, applied at this hospital; all but 2 with advanced disease received a complete external irradiation followed by transvaginal roentgen therapy.

Four of these patients died of intercurrent disease and without signs of recurrence before 3 years had elapsed following treatment. Three other patients are at present living with apparent recurrences or metastases. Thirty-five patients have died of cancer or in circumstances that do not permit the assurance that cancer was not the cause of death. Thirty-four patients, or 44 per cent of the total number of patients applying for treatment, remain well and without symptoms of recurrence after a minimum control of 3 years. Since some of these patients (4 to 7 according to probability) may have recurrence in the next 2 years, these results should not be compared with 5-year statistics from other sources.

The main advantages of this form of treatment are lesser infectious and urinary complications, a low incidence of fistulas and an apparent reduction in the proportion of local recurrences; in addition, this method of treatment does not require hospitalization. 8 figures.

(The comparatively few reports on the employment of transvaginal roentgentherapy for cervical carcinoma by such men as Merritt, Behney and others, indicate the definite comparability of its results with other forms of irradiation therapy, although it does not appear to be established that it is an essential adjunct of external irradiation. The especial advantages claimed for it in the treatment of cervical stump cancer seem somewhat more impressive, but even this would probably not be conceded by all workers in this field.—Ed.)

LATE RECURRENCE OF CERVICAL CARCINOMA FOLLOWING RADIATION THERAPY

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Am. J. Obst. & Gynec., 55: 533–537, 1948

The purpose of this paper is to record 2 cases which show that cervical carcinoma may progress slowly, or perhaps even lie dormant for long periods after treatment by irradiation, during its later clinical stages.

The first patient was a 52-year-old nullipara who had been treated for primary carcinoma of the cervix at the age of 35 years. The uterus at that time was moderately movable but there seemed to be some shortening of the right parametrium. Biopsy report stated "epithelioma, type uncertain." Treatment consisted of radon administration and low voltage pelvic x-ray. The patient was under observation for $12\frac{1}{2}$ years, during which time there was no evidence of residual or recurrent tumor.

On the present admission she complained of vomiting, diarrhea and lower abdominal pain of 18 days' duration. A hard irregular mass occupied the right lower quadrant and the vagina was filled with hard friable tumor. The patient developed a toxic erythema and died a month after admission. At autopsy the anatomic diagnosis was "carcinoma, primary in cervix, with extension to fundus, bladder, rectum, ovaries, Fallopian tubes, and metastatic invasion of periaortic lymph nodes, liver and diaphragm; ureteral obstruction, bilateral, with hydroureter and hydronephrosis." The pathologist compared sections of this tumor with that of the original cervical biopsy of $17\frac{1}{2}$ years previously and stated that one could not be distinguished from the other, so similar were they in histologic detail.

The second patient was first admitted to this hospital at the age of 33 years with a large, lacerated, eroded, discharging cervix. Histologic examination of cervical tissue revealed epidermoid carcinoma. The patient was given radium and x-ray treatment and was followed at regular intervals for 6 years. She was not seen again until the age of 53 years. She now stated that for the past few years she had experienced a foul, blood-tinged vaginal discharge. A hard, friable tumor mass was found to involve the cervix and adjacent vaginal walls with slight fixation of the parametria. Biopsy showed epidermoid carcinoma, grade

III. Deep x-ray treatments were given. She was readmitted in 3 months, the tumor having extended to the bladder and rectum. There was blockage of the right ureter by the tumor. The patient died within a few months.

The author states that it is impossible to prove that the secondary cervical tumors in these 2 cases represent recurrences rather than independent cancers. However, the fact that the histologic types of the secondary tumors correspond with those of the original biopsy specimens makes the presumption reasonable that these were long delayed recurrences of previously treated cervical cancers.

The average interval between treatment and recurrence in 105 patients with recurrent epidermoid carcinoma of the cervix treated with radium at this hospital was 14.5 months. Fifty-seven per cent of the patients manifested their tumor recurrence within a year. Only one recurrence was observed after 5 years.

(Such vagaries in the behavior of cervical carcinoma as are illustrated by the 2 cases reported by Speert are encountered by everyone who treats many cancer cases, and they are not peculiar to cervical carcinoma, being observed also with cancer of other organs. They are not easy to explain, except on the speculative basis of unknown body resistance factors, or the more logical one of local resistance to cancer cells through their entrapment by radiation-fibrosis and their later escape and reactivation. This is of course purely hypothetical. —Ed.)

CARCINOMA OF THE CERVIX TREATED BY COMBINED RADIATION AND SURGERY

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The high percentage of recurrence of cervical cancer in patients receiving radium and x-ray therapy alone brought about the feeling that the results could possibly be improved. With cases not too advanced, the author believes that a primary course of extensive local irradiation with radium, possibly followed by x-ray irradiation, and subsequent total hysterectomy offers the patient the greatest possibility for a permanent cure. In the past 5 years there have been performed 23 total hysterectomies following radium therapy.

At the present time, the author uses 50 milligrams of radium over a period of 108 to 120 hours, the total dosage being from 5400 to 6000 mg. hours. A small amount of radium over a long period of time seems to produce much less radiation cystitis or proctitis than larger amounts applied for a shorter period. Six to 12 weeks following the initial course of radiation, a bilateral salpingo-oophorectomy and total hysterectomy are performed. The technic used is that described by Foss (Surg., Gynec. & Obst., 76: 214, 1943) and the author. The right angle

clamp is used, removing as wide a vaginal cuff as possible. The broad ligaments, parametria and upper part of the vagina are resected as widely as possible. In many cases search has been made for nodes, as described by Taussig, with failure to find them. The writer believes the nodes most likely to become involved are those immediately lateral to the cervix, which are usually removed, rather than those along the hypogastric vessels.

In comparing these 23 cases treated by surgery following irradiation with 41 cases of cervical carcinoma treated with irradiation (radium and x-ray) alone over the same 5-year period, the following results are seen:

RADIUM AND SURGERY		RADIUM AND X-RAY
17	Living and well	10
1	Palpable recurrence	13
2	Dead	12
3	No follow-up	6
23	Total	41

Probably it is unfair to compare these 2 groups statistically. Many of the patients receiving only radiation were considered to be unsuitable for surgery. The number with palpable recurrence is the significant group. The removal of the uterus and cervix lessens the likelihood of recurrence, it is believed. Many of the cases in the radiation group were League of Nations, Group III, at the time of original examination. Some of the patients having a hysterectomy were League of Nations, Group III.

Of the 2 patients of the 23 under study who have expired, one died from tuberculosis which had later become active. The other, when seen one month prior to her death, was found to have a "frozen pelvis" with extension into the base of the bladder and rectum. Two of the patients were operated upon over 5 years ago and show no evidence of recurrence.

It is of interest to note that while all the patients had positive evidence of carcinoma prior to irradiation, in only 3 of the uteri removed was microscopic evidence of active carcinoma found either in the cervix or in adjacent tissues. In all others, microscopic examination revealed only fibrous tissue or hyalin degeneration. Undoubtedly there is active carcinoma elsewhere in some of these specimens. The writer believes that many more than 3 in 25 would have had recurrence of the tumor if the uterus had remained in place.

It is concluded that the method of combined radiation and surgery for cervical cancer deserves further study, longer follow-up, and a larger series of cases before any positive statements can be made. A second report will be made later, giving the author's further experience.

(As the writer himself says, it would be unfair to compare the results in the 2 series of cases treated by 2 different methods for the reasons which he has himself advanced. Such papers as this only emphasize the fact that individualization of treatment is of the greatest importance in the management of cervical cancer. No one stereotyped plan can be applied;

if only one general plan were selected for all cases the safest and best for most clinicians would probably be radiotherapy.

But there are certain early cases in which operation, assuming the competence of the surgeon and the good condition of the patient, is probably to be preferred. With some this will mean some such form of modified Wertheim operation as that recommended by the author. With others it may mean even more formidable gland dissection than was practiced by Wertheim himself. Again, most gynecologists will probably not give preliminary radiation in the very early cases which they pick for operation; others, like the author, may think this an advantage. The sequence of preliminary radiation followed by operation is by some chosen more especially for the cases which do not respond favorably to operation. Occasionally, the radiation reaction in the vagina and parametrium is very unfavorable, producing brawniness and infiltration which may practically preclude later operation, as in a case which I recently saw in which this sequence had been tentatively planned.—Ed.)

THE EVALUATION OF THE RESULTS OF CARCINOMA OF THE CERVIX UTERI TREATED BY RADICAL VAGINAL OPERATION

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The author prefers the radical vaginal operation instead of the radical abdominal operation for the following reasons: 1. the primary mortality is much less; 2. stocky, plump and adipose patients can be more effectively tackled by the vaginal route; 3. complications of the nature of urethral vaginal fistulae are much less frequent after vaginal operation than after the abdominal; 4. the end results after Wertheim's radical abdominal operation and Schauta's radical vaginal operation are practically the same; 5. although the regional lymph glands cannot be removed with the vaginal operation, this does not seem to materially effect the statistical end results; 6. the percentage of recurrence does not differ greatly after the 2 methods of operation; 7. a greater amount of parametrial, paravaginal, paravesical and pararectal connective tissue can be removed by the vaginal route with Schauta's incision than by the abdominal route; 8. lastly, the radical vaginal operation facilitates the introduction of radium in the parametrial tissue immediately or shortly after operation.

Special points of the technique of the operation are emphasized. The carcinomatous growth is cauterized with surgical diathermy on the day previous to operation. One-half per cent adrenalin with normal saline is injected into the left side of the perineum near the site of Schuchardt's incision. The vaginal cuff is one of the most important steps of the operation. It is meant not only to cover the growth of the cervix, but to excise along with it quite a large amount of vagina and paravaginal connective tissue proportionate to the extent of the growth. The Schuchardt's incision is generally made on the left side and it is

better not to make the incision in one sweep, but in different layers. If there is sufficient vaginal relaxation the vaginal cuff may be made first. However, if the vagina is narrow or the pelvis is one of anthropoid or android type, or the growth is still a big one after cauterization, the Schuchardt's incision is made first. The ureter should be dissected freely and displaced laterally and upwards in order to make possible the removal of the maximal amount of the parametrial tissue. The dissection should be made by small steady and careful cuts with a pair of scissors, and not merely pushed laterally without making any clear-cut demonstration of its topographical anatomy. It is dangerous to make a blunt dissection with gauze even if there is infiltration of the parametrial tissue. By opening the uterovesical pouch the uterus is brought forward and separated with the appendages. By pulling down on the uterus with a strong pair of vulsellum forceps and the cervix by means of the traction thread, a wide cut of parametrial tissue is removed on each side. Of the 151 patients operated on by this technique since 1932, 6 died of the operation, a primary mortality of 3.8 per cent; 3 patients died of shock, 1 of pulmonary embolism on the 14th day, 1 of pneumonia, and 1 of staphylococcus septicemia. The bladder was injured in 6 patients, of whom 2 required an operation for perfect recovery, whereas fistulae healed spontaneously in 4 other cases. In 23 per cent of the patients the Schuchardt's incision did not unite by first intention but later healed by granulation. Bacillus coli infection is a common factor during the postoperative period to the extent of about 54 per cent. Prior to 1940, 93 cases were operated upon and the 5-year salvage totalled 35 cases, a relative cure rate of 37.6 per cent. The operability was estimated at 57.7 per cent, although all cases that could have been operated upon were not treated by operation. Dividing the cases according to the League of Nations Classification, the 5-year relative cure rates were 61.5 per cent of Grade 1, 44 per cent of Grade 2 and 15.6 per cent of Grade 3. These figures compare favorably with results of radiation therapy.

In conclusion the author appropriately quotes a few lines from Bonney: "So far as operation is concerned, apart from its effect on carcinoma of the cervix, it has been and still is a great educational factor in gynecology, and it has raised the reputation of gynecologic surgeons in the opinion of surgeons in general, for the procedure is the most difficult of all surgical procedures. It has taught us the anatomy of the pelvis in a way that no dissecting room preparations could possibly have taught, and it has enlarged the surgeon's vision, so that, though in the future we may quite possibly see it replaced by a treatment more efficient, its disappearance from the field of gynecology will not be an entire gain."

(The radical vaginal operation for cervical carcinoma must be compared only with the so-called modified Wertheim operation, which aims only to add to abdominal panhysterectomy and bilateral salpingo-oophorectomy, the removal of as much parametrium as possible and the removal of a large cuff of vaginal mucosa. Since the latter is the operation which is most frequently done in this country in the small proportion of cases in which surgery is thought to be justified, the basis of comparison is a fair one.

In this country the abdominal route has always been the popular one, but for many years the German, Austrian and Hungarian clinics especially have been partial to the vaginal operation. It would be difficult to argue against the first 4 of the advantages claimed for it

by the author, assuming that the operator is thoroughly trained in its technique. I must confess that the operations which I saw done by this method in the continental clinics seemed to me to have some advantages over the abdominal operation, although I myself, like practically all American gynecologists, had always employed the abdominal route. It seemed easy to visualize and to avoid the ureter, and probably easier to remove a considerable portion of the parametrium from below than from above. Any amount of vaginal mucosa can of course be easily removed from below, much more so than from above, and this is a not unimportant consideration.

Many of the pros and cons which apply in the controversy as between abdominal and vaginal hysterectomy for benign conditions apply also to the question of cancerous disease, one or the other route being favored by most operators because they have practised it more or less routinely and have therefore become more proficient in it. There would seem to be no very striking difference in the ultimate results.

For those more ambitious operators who include wide dissection of the pelvic glands there is no choice, since only the abdominal route permits of this. However, the advantages of these very radical operations are still to be demonstrated, and radiotherapy is still the method of choice for the vast majority of cervical carcinoma patients. Only the Stage 1 patients, and, in the practice of some gynecologists, some of those in Stage 2, would seem to justify surgery at all, and this only when the surgeon is trained in the difficult technique of these formidable operations. For the great majority of gynecologists, I believe that radiotherapy is the wisest plan except in the occasional very early case in which the patient is a good operative subject otherwise. In this very small group, moreover, the so-called modified Wertheim operation will be safer in most hands than will the extensive gland operations which are being done in a few clinics in the effort to determine whether an improvement in the cure rate can be obtained which will more than offset the greater hazard of such operations.—Ed.)

UTERINE BLEEDING ASSOCIATED WITH UREMIA; REPORT OF TWO CASES

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The authors were unable to find in the literature any previous references to bleeding per vaginam resulting from uremia. Two cases are presented which describe this phenomenon. The first patient was admitted as a gynecologic diagnostic problem, while the second patient developed vaginal bleeding while under treatment for uremia. Both patients were colored; their ages were 27 and 43 years, respectively. At autopsy, both patients' uteri showed a thin endometrial lining; in the first case the glands were characteristic of the early proliferative phase.

In the first case the vaginal bleeding was severe, requiring packing and blood transfusion. The second case presented the findings of gastrointestinal hemorrhage not infrequently encountered in the uremic state. In addition, a very definite vaginal hemorrhage accompanied the bleeding diathesis, though the degree of exsanguination from this source was not as great as in the first case.

In what way this terminal state of renal decompensation brings about hemorrhage from the endometrium is difficult to explain. Since vaginal bleeding has often been a part of some blood dyscrasia and is, at times, without hormonal explanation in some cases of metropathia hemorrhagica, it remains at present to indict the vascular system of the uterus itself for the bleeding.

(I suppose that the natural question which many would raise concerning these 2 patients would be whether the bleeding in these uremic patients was actually due to the uremia or whether it was coincidental. In the first case the latter would seem to be the more likely explanation, especially as neither gynecologists nor internists have ever, so far as I know, considered uterine bleeding a possible symptom of uremia. The finding of a thin, early proliferative type of endometrium would not be at all incompatible with a simple functional type of bleeding. The possibility that the terminal uremia in the second patient might, through vascular damage or blood changes, have been responsible for the bleeding, seems less remote.—Ed.)

ABNORMAL UTERINE BLEEDING

E. J. Bateman

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The writer summarizes the management of abnormal uterine bleeding as follows:

The physician confronted by a patient complaining of abnormal bleeding should immediately think of the possibility of cancer. He should next think of the possibility of pregnancy, threatened abortion, postabortal bleeding, or ectopic pregnancy. He should take a careful history of the complaint and everything possibly connected with it. He should make a careful and thorough pelvic examination in all patients, including biopsy of every suspicious cervix. He should institute appropriate treatment for any inflammatory or surgical condition.

If the findings on palpation and bimanual examination are negative, the bleeding is to be regarded as functional and, if not excessive and if the patient shows no appreciable ill effect from it, she may be treated for a reasonable length of time by general tonic measures, endocrine and biologic products. If these measures fail, and they frequently do, the uterus should be thoroughly curetted.

The patient should be curetted at once if the bleeding is excessive, if it is due to recent abortion, or if she is at, near or past the menopause. In the latter case, radium is frequently indicated.

Hysterectomy with preservation of the ovaries is usually the treatment of choice if curettage fails to cure the patient between the age of 35 and the early forties. Radium, if not contraindicated, is preferable for those at or near the menopause.

Panhysterectomy is the only satisfactory treatment for cancer of the fundus, preceded by radiation only in the presence of definite indications. If the uterus is still small and freely movable, and the patient in good condition, the writer believes that operation should be done at once.

The writer concludes by warning that the physician must be careful not to produce abnormal bleeding by the overuse of estrogenic products.

(A simple but sound review of the general principles in the treatment of abnormal uterine bleeding. The age limits suggested by the author for the performance of hysterectomy in preference to radiotherapy in cases of intractable bleeding, seem fair enough, although individual exceptions are at times justifiable. The prevailing plan of treatment of adenocarcinoma of the corpus is irradiation followed 6 or 8 weeks later by panhysterectomy, but I agree with the author that this should not be a hidebound rule in operable cases. When the preliminary curettage, especially in postmenopausal women, reveals what even on macroscopic examination is obviously a body carcinoma in an early stage, or when this diagnosis is confirmed by good frozen sections which are often possible with the fairly abundant curettings yielded in such cases, I also would usually prefer to proceed with panhysterectomy at the same sitting. In such cases the cervical canal should be closed off with a mattress or figure-of-eight suture and clamps applied lateral to the uterus at the beginning of the abdominal operation, in order to avoid implantation of cancer cells in the vagina or peritoneum, or squeezing them into the lymphatics by the manipulations of the operation.—Ed.)

ENDOMETRIOSIS IN A YOUNG GIRL

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J. A. M. A., **136**: 690, 1948

The case reported by the author is, as far as he knows, that of the youngest girl yet reported in whom symptoms referable to endometriosis appeared. When this patient was 11 years old she had slight but definite pain in the lower left quadrant of the abdomen, lasting 3 or 4 days and recurring at monthly intervals. At her first menstrual period when she was 12 years old, this same pain occurred in greater degree and thereafter became more severe with each menstrual period. Treatment with sedatives, estrogens and other medications was useless. Finally, one physician sent the patient in for resection of the presacral plexus. Endometriosis was not diagnosed until the time of operation, although dysmenorrhea, increasing each month, should have served as a diagnostic point.

At operation the omentum was seen to be wrapped around a mass attached to the left cornu of a bicornate uterus. There was a smaller separate mass on the anterior surface of the left broad ligament. The pathologic diagnosis was endometriosis. Neither ovary was involved. The larger mass was made up of several small cysts filled with chocolate-colored substance.

There was no pain during any of the 3 menstrual periods since operation. The

periodic pain occurring for 8 months before the menarche is suggestive of cyclic changes in the endometrium before actual bleeding begins.

(From the author's description I would be inclined to doubt that this case was one of pelvic endometriosis as the latter is commonly understood. The patient had a bicornate uterus and in such cases one may encounter various anomalies as a result of imperfect development of one of the uterine cornua. Its lumen may be shut off at one or more points or, for that matter, such a rudimentary horn may consist of a mass of uterine muscle in which endometrial glands are scattered, constituting a species of adenomyoma. When the lumen of the imperfect horn has no communication with the cavity of the other more highly developed horn, it is sometimes filled with menstrual blood, and a blood-containing cyst of this sort, lined as it is with endometrium, is easily mistaken for an ordinary endometrial cyst.

I can illustrate what I mean by citing a recent case of my own. The patient, age 16, had suffered with unusually severe and prolonged dysmenorrhea which had not been appreciably ameliorated by the variety of drugs and hormones she had received, so that pelvic sympathectomy was decided upon. At operation there was, as in the author's case, a bicornate uterus. One horn was well developed and to its upper portion was attached what at first looked like an endometrial cyst of the left ovary, until the left ovary was demonstrated as entirely normal and quite separate from the small mass just described. Microscopically the wall of the latter was made up of a thinned out layer of uterine muscle, lined by endometrium.

I have been a bit surprised at the emphasis of one or two authors on the occurrence of endometriosis in young girls in their teens. This has certainly not been a frequent observation in our own material, and I have wondered if this difference could be interpreted as due to differences in microscopic interpretation.

The microscopic demonstration of ectopic pelvic endometrium usually offers no great difficulty and it should be the basis of diagnosis, suggestive and characteristic as the gross appearance of endometrial cysts is at the operating table. As a matter of fact, unless the blocks are cut before fixation, small areas of endometriosis are often missed in the laboratory examination of the fixed specimen.—Ed.)

TUBERCULOSIS OF THE UTERINE CERVIX

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Excepting the vulva, tuberculosis of the uterine cervix constitutes the less frequent bacillary infection of the female genital tract. After analyzing the age incidence, frequency, way of infection, symptomatology, differential diagnosis and treatment of this type of lesion, the authors report a case which was successfully treated. A 45-year-old female sought medical treatment for slight vaginal bleeding. At the age of 12 she was treated for what seems to be Pott's disease. Pelvic examination revealed a polypoid formation on both lips of the cervix, surrounding the external os of the latter, and showing contact bleeding. A biopsy was made, which confirmed the impression of tuberculosis of the cervix. Submitted to laparotomy, a caseous nodule was encountered in the pouch of Douglas and another one was seen on the right tube, close to its isthmic portion.

Operation consisted of pan-hysterectomy and bilateral salpingo-oophorectomy. Pathological examination revealed an old tuberculous lesion in the right tube and a tuberculous nodule in the pelvic peritoneum, both in the stage of cicatrization. The endometrium presented a normal aspect. In this case, therefore, a typical tuberculosis of the uterine cervix, the infection probably originated in the tube and peritoneum and, following the descending route, reached the endocervix. Six months later the patient was in very good condition.

(Tuberculosis of the cervix, in the fairly advanced stage described by the authors, is rarely seen, since it is practically always a late phase of a tuberculous process beginning in the tubes and later involving the endometrium before it reaches the cervix, so that the patient is likely to have sought treatment before the cervix is involved. In the relatively rare cases of cervical tuberculosis which have been reported, however, the gross resemblance to carcinoma has often been striking. In a former day, when biopsy was often used only for confirmatory purposes when the cervical lesion seemed obviously cancerous, and sometimes not even then, it is easy to understand that the surgeon was occasionally surprised to get a pathologic report of tuberculosis instead of cancer.

When the patient's condition permits, the proper treatment is total hysterectomy, with removal of both tubes, although conservation of one or both ovaries is often permissible when they show no gross involvement. As in all tuberculous pelvic cases, the postoperative treatment should emphasize the general hygienic regime so essential in the management of any type of tuberculosis.—Ed.)

UNSUSPECTED TUBERCULOUS ENDOMETRITIS

J. R. O'BRIEN AND M. K. LAWLOR

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The type of tuberculous endometritis discussed in this paper is that *occurring in patients who are not obviously ill, but who complain of sterility or menstrual irregularity.* On investigation they are not found to have any clinically detectable abnormality in the pelvis or elsewhere, yet histological examination reveals the presence of tubercles in the endometrium.

During the last $8\frac{1}{2}$ years, 3,600 curettings were examined for all purposes, and tuberculous endometritis was found in 37 curettings from patients with no evidence of pelvic tuberculosis, an incidence of 1.03 per cent. .These 37 curettings were obtained from 23 patients, giving an incidence of 0.59 tuberculous patients per 100 patients so examined. Of these 23 tuberculous women 17 complained of sterility, giving an incidence of 1.89 sterile patients per 100 curettings from the infertility clinic.

All 23 cases occurred in the reproductive age. The primary complaint of 6 was menstrual irregularity; the remaining 17 complained of sterility, and 9 of these also had menstrual disturbances. In no case had pregnancy occurred within 10 years of the diagnosis, nor has any pregnancy been reported in the follow-up. A chest x-ray showed no evidence of gross pulmonary tuberculosis in any case.

Of the 23 cases, 17 remained apparently well while under observation; in 5 local spread occurred, which was treated by total hysterectomy and bilateral salpingo-oöphorectomy; and one case not submitted to operation died of miliary spread. The danger of spreading the disease by tubal insufflation is emphasized.

As the diagnosis can be made only on histological examination of curettings and the diagnostic tubercles may be rare, all the fragments of endometrium obtained at curettage should be examined routinely. Serial sections should be taken through the block when there is a history of some other possible tuberculous lesion, or when initial examination shows diffuse lymphocytosis, lymphoid aggregates or fibrosis. Examination of such curettings should always include either culture or guinea-pig inoculation.

Examination of sections in the present study did not help to resolve the question of whether the endometrium is reinfected each month from an occasional tubercle remaining in the basal layers which escapes being shed, or from the Fallopian tubes. In every case in which the tubes were examined histologically they were always found to be infected, thereby lending some support to the second hypothesis.

The correct method of treatment of tuberculous endometritis is still uncertain. If it is believed that miliary spread in the fatal case arose from the endometrium then it might be justifiable to perform total hysterectomy and bilateral salpingo-oöphorectomy on every case. On the other hand, miliary spread appears to be rare, and normal health over long periods is common; therefore, it is probably wiser to be watchful and conservative and to treat each case on its own merits.

(In a paper previously abstracted in the Survey, Sharman of Glasgow reported an incidence of 5 per cent of endometrial tuberculosis in the routine examination of endometrial biopsy material removed in the study of female sterility (Proc. Roy. Soc. Med. (Sect. Obst. & Gynec.), 37: 6772, Dec. 1943. Abst. in Survey, 1: 149, Feb. 1946). This rather startling figure, as I remarked at that time, was certainly much higher than noted in my own experience, and probably also that of other gynecologists, and yet just this same incidence was reported more recently by Schockaert from the Louvain Clinic.

Most of our endometrial biopsy studies are directed to 2 points; first, to determine whether or not the patient has ovulated; and, secondly, to evaluate the endometrial response to the ovarian hormones. In most laboratories, therefore, only one or two good sample sections are examined, and they are probably sufficient to allow an intelligent appraisal of the above mentioned points. An occasional unexpected tuberculosis will be revealed, the incidence reported by O'Brien and Lawlor (0.59 per cent) being probably closer to the experience of most of us than the figure reported by Sharman and Schockaert.

On the other hand, it is quite probable, as the authors of the present paper emphasize, that if the biopsy material were examined through numerous or serial sections, a much higher incidence of tuberculosis might be revealed than most of us would suspect. Furthermore, it must be remembered that many endometrial biopsies, especially those done by the punch methods, yield only small bits of endometrium. This is one reason why I prefer the curetting methods, and, naturally, the suction curette devised by myself. It is just about as easy to scrape the entire or almost the entire mucosa as to get only a small strip or two, and in most cases I do just that. The abundant tissue thus obtained gives a far more comprehensive idea of endometrial histology and pathology than does the examination of a small isolated bit of tissue. It is quite possible that if we make a good many sections of this material, as we are now beginning to do, we may find unsuspected tuberculosis more often than we have in the past.—Ed.)

THE ADNEXA

SPIRAL ARTERIES IN THE HUMAN OVARY

B. Delson, S. Lubin and S. R. M. Reynolds

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Endocrinology, **42**: 124–128, 1948

Spiral arteries have been observed in the hilus of the human ovary. These were demonstrated by means of plastic injection-corrosion preparations. These confirm in every detail the original and forgotten description of these structures by Farre in 1858.

Preliminary observations suggest a relationship between distortion of the spiral blood vessels and certain types of ovarian pathology. For instance, in the rabbit, in the presence of *corpus* hemorrhagicum cysts, there is distortion of the spiral artery during the period of follicular enlargement. Preliminary study of human preparations shows marked differences in the vascularity of corpora lutea and of follicular cysts. Likewise, there are striking alterations in sclerotic ovaries. 3 figures.

(The senior author (Reynolds), who has done much good work in the experimental study of reproductive phenomena, especially uterine motility, has been much interested in these newly-rediscovered spiral arteries in the human, although their exact role in the mechanism of the cycle is still anything but clear.—Ed.)

GRANULOMA OF THE FALLOPIAN TUBE DUE TO SURGICAL GLOVE TALC; SILICIOUS GRANULOMA

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Brit. J. Surg., **34**: 2–8, 1947

Seven cases of silicious granuloma are described, 2 occurring in appendectomy scars and 5 in the Fallopian tubes. All occurred in cases that had undergone a previous laparotomy, and microscopy revealed the presence in all the lesions of doubly refractive material which is considered to be talc deposited at the earlier operation.

All 5 of the cases in which the lesion occurred in the Fallopian tube had undergone a previous laparotomy for appendicectomy and, apart from an abortion in one patient, all patients were subsequently sterile. The symptoms were sug-

gestive of a low-grade pelvic inflammation and physical examination revealed thickened tender Fallopian tubes. Only one patient gave a history of a possible tuberculous infection elsewhere, having had cervical adenitis 2 years previously. No abnormal findings were noted on clinical examination. No history of gonococcal or syphilitic infection was obtained and the sera from all patients gave a negative Wassermann reaction.

As to differential diagnosis from tuberculosis of the Fallopian tube, it would seem reasonable in the microscopic examination to accept as primarily silicious a giant-cell granulomatous reaction, with scanty or absent endothelioid cells, absence of caseation, and the presence of doubly refractive material within or closely related to the giant cells. The present series of cases showed few, if any, cells that would be properly classified as endothelioid.

Morphologically, the foreign bodies are most commonly spicules of various lengths, although when within the giant cells they are frequently rounded. The spicules have the size and shape of talc and are also proved to be silicious by the method of Belt and Ferris (1942).

The development of the lesion in the Fallopian tube is presumably similar to that described in traumatic and post-operative silicious granuloma. The possibility is raised that the talc left in the peritoneal cavity at operation may become concentrated in the Fallopian tubes. Once there, the particles penetrate the epithelium and set up a foreign-body granulomatous reaction.

Several of the tubal lesions had been previously diagnosed as tuberculous and the question is raised whether some cases diagnosed histologically as tuberculosis of the endometrium may not, in fact, be also silicious granuloma.

It is only by recognition of the dangerous potentialities of talc and by a total avoidance of its use that the unfortunate sequelae can be prevented. 8 figures.

(In our own country this question of talc granuloma from the commonly used surgical glove dusting powder has been agitated especially by Major Seelig and his coworkers, their most recent complete publication having appeared in 1943 (J. A. M. A., 123: 950, 1943. This article also gives references to previous publications on the subject.) Although they showed quite clearly that granulomas, especially of the peritoneal surfaces, with often the development of peritoneal adhesions, may follow the use of talc powder, it has seemed to me that their studies have been passed over rather lightly by most surgeons. I have talked this over at times with some of my colleagues, and find that none of them has been impressed with any especial hazard from the use of talc powder. This certainly does not negate its possibility, especially since such undesirable sequelae as adhesions occur from various other causes, so that the responsibility of talc cannot be demonstrated without studies aimed intensively on this point.

On the other hand, I am sure that all surgeons would cheerfully adopt dusting powders, such as the potassium bitartrate recommended by Seelig, if the matter were forcefully brought before them as a result of education of hospital authorities, surgical committees, and perhaps commercial interests which would further publicize hazard-free surgical dusting powders.

The fact that Roberts could report from one clinic the finding of 5 cases of what is apparently a clearly established granulomatous salpingitis is rather startling, especially since previous studies had not envisaged the tubal mucosa as one of the sites for such involvement. The photomicrographs accompanying his article (Cases 5 and 6) are also rather disquieting in that they show a picture which would unquestionably be diagnosed as tu-

berculous salpingitis by most pathologists. It was only by the employment of special methods, especially the use of the polarizing microscope, that the distinction could be made and the "silicious" nature of the lesion established. It would probably be a good plan for all of us to review cases of tuberculous salpingitis in our laboratories from this standpoint.—Ed.)

BILATERAL OVARIAN DERMOIDS IN A GIRL OF TWELVE

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J. Obst. & Gynaec. Brit. Emp., 54: 657–658, 1947

A 12-year-old girl was admitted complaining of intermittent attacks of abdominal pain and vomiting for 3 months. Colicky pain was at first in the center of the abdomen; later it had shifted to the right iliac fossa. Menstruation had not yet begun.

Palpation revealed an ill-defined mass rising from the pelvis in the midline. *Per rectum*, a smooth, spherical mass almost filling the pelvis was felt behind a small mobile uterus.

At laparotomy, a pedunculated right ovarian cyst, 4 inches in diameter, was found, and was removed. No ovarian tissue was recognizable, so none could be conserved. The left ovary contained several retention cysts and a larger cyst, ¾ inch in diameter. This larger cyst and a few of the smaller ones were removed, leaving a portion of the ovary. Recovery was uneventful.

Microscopically, the wall of the right dermoid showed a stratified, squamous epithelial lining. Accessory skin structures were present: hair follicles, sweat glands and sebaceous glands. The lumen contained keratinous material and hairs. The left dermoid cyst consisted of a fibrous tissue wall lined by stratified squamous epithelium. Accessory skin structures were not present. Flaked-off keratin lay in the lumen.

(Bilaterality of dermoid tumors is not rare, being noted in approximately 10 per cent of all cases. Since so many of the patients are young, conservative surgery is indicated in practically all these patients. In a recent case of my own, one ovary was completely replaced by a dermoid the size of an orange, while the other ovary contained one as large as a golf ball. On the latter side, however, there was considerable ovarian parenchyma still present, its essentially normal function being indicated by the presence of an almost mature corpus luteum. Since dermoid cysts are benign, with only a comparatively slight incidence of secondary malignant change, conservative surgery is fully justified, and especially in cases of the bilateral type. Where one side only is involved in a tumor of considerable size, most of us would prefer to remove the neoplastic ovary completely.—Ed.)

DYSGERMINOMA OF THE OVARY

B. KAREN AND J. I. KUSHNER

Bronx Hospital, New York, N. Y.

Am. J. Obst. & Gynec., 55: 337–339, 1948

The writers present the case of a 26-year-old female who complained of pain in the right lower quadrant of 4 days' duration. The past history was irrelevant. She had been married 4 years, with no pregnancies.

Examination revealed a palpable, irregular mass occupying the entire left lower quadrant. The external genitals were normal. The uterus was not palpable. The right adnexa showed a tender palpable ovary.

At operation the left adnexa was found to be the seat of a large, irregular, nodular solid mass. The uterus was small. The right ovary was enlarged and cystic, with its Fallopian tube kinked. Supravaginal hysterectomy and bilateral salpingo-oöphorectomy were performed. Recovery was uneventful.

Microscopically, sections of the ovary revealed clusters of round or ovoid cells with clear, acidophilic, sparse cytoplasm arranged in alveoli and separated by a hyalinized connective tissue stroma. Large areas of necrosis were present. Section of the other ovary revealed several follicle cysts, one of which was filled with acidophilic secretion. Several corpora albicantes were present. The diagnosis was dysgerminoma of the ovary. 2 figures.

(The exact degree of malignancy of dysgerminoma is still difficult to put statistically. These tumors are unquestionably much less malignant than the common varieties of primary carcinoma, such as adenocarcinoma or papillary carcinoma. This fact, together with the fact that they so characteristically occur in young women, in whom preservation of the childbearing function is important, justifies conservative operation when the tumor is not very large and when it is well encapsulated. As a matter of fact, under such conditions the surgeon is likely to think that he is removing a benign fibroma, especially as the rarity of dysgerminoma makes many gynecologists unfamiliar with the gross appearance. They are apt to be surprised when the pathologist reports dysgerminoma, and the question which then presents itself is whether to do a secondary radical operation, resort to radiotherapy, or simply to mark time and watch the patient's subsequent course. Under the conditions enumerated above, the last-named is usually the best plan.

On the other hand, if the tumor is large or has infiltrated through its capsule, radical operation is clearly indicated, with radiotherapy afterwards. Reports as to the degree of radiosensitivity differ somewhat, but the majority indicate a considerable degree of responsiveness. The study of a comparatively small group of these cases in our laboratory a good many years ago showed a recurrence rate of something like 25 per cent. In a recent case in our department radical operation was followed rather quickly by extensive mediastinal metastasis, the autopsy showing that this was the only metastasis which had occurred. Some of these tumors, therefore, are of a high degree of malignancy.—Ed.)

EMBRYONIC TERATOMA

P. BARATA RIBEIRO AND J. BICA

Rio de Janeiro, Brazil

Obst. Gin. Lat.-Amer., 5: 103–110, 1947

The authors analyze the etiology, clinical course, diagnosis, prognosis and treatment of embryonic teratomas of the ovary. They then present the clinical history and histopathological study of such a case. The patient, a 10-year-old Negro girl, presented a neoplasm the size of a grape-fruit, free and movable, in her right ovary. Following an unilateral salpingo-oöphorectomy, deep x-ray treatment was administered, and 9 months later the patient had gained in weight and her general condition was greatly improved. There were no signs of recurrence.

(As there are no details in this abstract as to the histologic structure of this "embryonic teratoma" it is difficult to be sure whether it was of the type of simple cystic teratoma represented by the ordinary dermoid, which not infrequently contains derivatives of other fetal layers than the ectoderm which explains the presence of skin and such skin appendages as sebaceous and sudoriferous glands and hair follicles. From the fact that the term "embryonic teratoma" is used, it may be assumed that the structure was the more complex one of a solid teratoma, representing all 3 of the fetal layers, and often in the undifferentiated, embryonic form which makes these tumors so highly malignant in contrast to the simple dermoid. Such tumors almost always occur in young patients, often children, and most of them are fatal, so that, after only 9 months, one cannot be sure of the later course in the case reported by the author. It is doubtful whether postoperative radiation in cases of this group exercises any decisive influence in the outcome.—Ed.)

OVARIAN CONSERVATION DURING SURGERY; WITH REFERENCE TO BILATERAL DERMOIDS AND ENDOMETRIOSIS

A. A. LEVI

Boston

New England J. Med., 238: 83–85, 1948

This paper is written to call attention to the benefits to be derived from ovarian resection, to supplement an article presented by the author in 1939 and to make a plea for greater conservatism on the part of the surgeon dealing with ovarian surgery.

In the paper referred to, the case of a 33-year-old patient was discussed. The ovaries were nearly the size of large oranges because of bilateral dermoid cysts. At operation, the right ovary was removed completely. The left was resected; a piece 1.5 cm. in diameter and as thin as a dime remained. Since the operation

in 1938, the periods have occurred regularly without undue event. Frequent pelvic examinations have disclosed no change in the residual ovarian tissue.

When a second patient with bilateral ovarian dermoid cysts presented herself, she was also treated conservatively. The patient, aged 28 years, reported for a premarital examination. Bilateral ovarian dermoid cysts were found. At operation the right ovary was completely removed. A small piece of normal-appearing tissue was located in the left ovary near the ovarian vessels. This piece, hardly larger than a dime, was left in place. Two weeks after operation a regular period occurred, and the patient completed her plans for marriage. Subsequently she was delivered of 3 healthy well formed babies. These 2 cases demonstrate that adherence to the advice in the older textbooks "to remove both ovaries in cases of bilateral dermoid cysts" not only is unwise but also may be calamitous.

Martzloff concluded that out of a total of some 200 cases of dermoid cysts in one or both ovaries, there were only 2 cases of carcinoma developing in an ovarian dermoid cyst. This remark disproves effectively what is written in textbooks as dogma: that most ovarian dermoid cysts become malignant, which they obviously do not. Other writers are quoted because their papers express the wisdom and ease of conserving ovarian tissue.

Two additional cases of endometriosis are reported, both with endometrial implants and involvement of both ovaries. In each, one ovary was removed. The remaining ovary was partially resected. Both patients were subsequently delivered of normal healthy babies and had regular painless periods after these deliveries.

In the treatment of a large number of women over a period of 17 years, the author has practiced conservative surgery in numerous cases, and the final results have been most gratifying.

The 4 cases described were chosen as the most suitable to drive home the point that conservative ovarian surgery is possible and ultimately pays large dividends to the patient.

(As to the desirability and importance of ovarian conservation in women during the reproductive period of life, and especially those of the younger age group, there can be no question. This conservative trend should be extended to apply also to the uterus and tubes since the retention of the childbearing function is so often an important consideration in such patients. However, it is possible to make such a fetish of conservatism as to make it an ill-advised procedure in some cases. Certainly no criticism can be made of the conservative plan employed by the author in his 2 cases of dermoid cyst, and certainly we should always try to avoid radical operation, with removal of all ovarian tissue, in the treatment of endometriosis in young women. In patients who have already had one ovary removed, there is all the more justification for the conservative plan in dealing with benign lesions, such as dermoids, in the remaining ovary.

However, it is not always genuine conservative treatment to resect "cystic" ovaries which would have been better let alone, or to leave fragments of ovarian tissue involved in a tubo-ovarian abscess when the other ovary is relatively normal. It is surprising how often, in taking gynecological histories, one learns that a patient has previously had an appendectomy and resection of a cystic right ovary. One is impelled to think, very unkindly no doubt, that the surgeon had not been sure whether the patient's right sided pain had been

caused by the appendix or the ovary, and thought it best to fire off a double-barreled gun by adding to the appendectomy resection of what was probably a normal ovary containing one or more harmless and normal cystic atretic follicles. Perhaps he even flattered himself that he was being conservative in not removing the whole ovary.

One occasionally hears the dictum that it is better to take an ovary out entirely or to leave it entirely alone. This of course is not a sound doctrine, but the nugget of truth residing in it is that partial resections should certainly not be done unless there is some good reason, such as a dermoid or a small endometrial lesion. I am sure that every surgeon has seen extensive adhesions of the intestine or of matting and angulation of the tube in the course of secondary operations on patients on whom resections of the ovary have been done, not to speak of cystic changes in the ovaries which were much more marked than those which had impelled the original resection. When only portions of an ovary are to be removed, the greatest care should be exercised to peritonealize as thoroughly as possible, because the leaving of raw and bleeding surfaces is a bid for such unpleasant sequelae as have been mentioned above.

Finally, it has seemed to me that the retention of the ovaries in women at or beyond the menopausal age, when hysterectomy is necessary, is not good conservatism, although I know that this is practised by some surgeons because they feel that the ovary has some function even after the menopause. If it has, no one has ever demonstrated it, and all clinical experience speaks against such a hypothesis. On the other hand, ovarian tumors, and especially the cancerous group, are fairly common, and the removal of functionless postmenopausal ovaries when hysterectomy is indicated is good cancer prophylaxis, without adding to the time or hazard of the operation.—Ed.)

OPERATIVE GYNECOLOGY

THE MANCHESTER OPERATION FOR GENITAL PROLAPSE

Sir W. F. Shaw

This writer discusses an article by Brentnall (1947) on Fothergill's colporrhaphy (abstracted in Survey, 3: 144,. Feb., 1948) in which Brentnall seeks to do honor to his old teacher.

Shaw claims that Donald was the first man in England to combine anterior and posterior colporrhaphy with amputation of the cervix, to use it regularly for the cure of genital prolapse and so successfully, that by the time the present author became a resident at St. Mary's Hospital in 1904, Donald's seniors as well as juniors were all performing a similar operation.

Donald began the operation by splitting the cervix and amputating both lips by wedge-shaped incisions. Having closed these he did the anterior colporrhaphy by marking out an oval area extending from just below the urethral orifice to a point fairly close to his cervical sutures. During the years of Shaw's residence Donald always laid great stress upon the suturing of deep tissues and he took a good bite of the tissue on each side of the cervix and tied them together in front of the cervix. In posterior colporrhaphy he began with the apex near the cervix and the base of the perineum, and here again he relied for a good result upon the deep suturing rather than on superficial skin sutures.

In 1906, Fothergill joined the staff as an Assistant Surgeon. He quickly realized what good results were being obtained by the use of this combined operation for genital prolapse and searched further on the subject for the reason. In 1907 he read a paper before the Royal Society of Medicine on "The Supports of the Pelvic Viscera; a review of pelvic anatomy with a clinical introduction."

Fothergill's operation was a modification of the original operation done by Donald. He called attention to important anatomical facts and the shape of his anterior colporrhaphy allowed these deep structures to be sutured more freely. He himself did not bury any sutures, but relied upon the vaginal skin sutures being placed deeply enough to pick up the important deep parts of the pelvic floor, eliminating the redundant tissue left by Donald's operation between the cervical incision and the anterior colporrhaphy, and also proving that the vagina need not be narrowed so much.

When the writer lectured upon this subject in America in 1933, it seemed too late to attach Donald's name to the operation, especially as he had never adequately described it in print, but it seemed unfair to attach to it the name of any subsequent operator who had merely modified the operation. Therefore, the writer suggested it preferable to use one term to cover all such operations which include a double colporrhaphy with amputation of the cervix and suturing

of the deep structures and, as the operation was developed in Manchester and has been continuously employed in that school for 59 years, it seems reasonable to employ the generic term of "The Manchester Operation."

(No one is better qualified than is Sir William Fletcher Shaw to discuss authoritatively the historical development of the procedure which has already come to be spoken of as the Manchester operation, since he, so to speak, grew up with the operation in the clinic in which Donald took the first steps along this line. Shaw later became the head of this same clinic, so that he, better than anyone else, was able to trace the later modifications by Fothergill and, though he modestly fails to mention this, also by himself. His suggestion that instead of calling the operation by the name of any one individual it be spoken of as the Manchester operation because it is the product of the Manchester School of Gynecologists, is eminently reasonable, and it has as a matter of fact been all but universally adopted in our own country as well as in most others.

The popularity which this procedure now enjoys in our own clinics is in large measure the result of the lecture of Shaw himself upon this subject in 1933, when he was the Honor Guest at the annual meeting of the American Gynecological Society. This paper was published in the American Journal of Obstetrics and Gynecology, 26: 667–686, 1933.—Ed.)

A MODIFIED METHOD OF SURGICAL REPAIR FOR PROLAPSE OF CERVICAL STUMP WITH ASSOCIATED ENTEROCELE

D. ROSE

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Am. J. Obst. & Gynec., 56: 346–347, 1948

In the case reported by the writer the patient was a 61-year-old multiparous white woman for whom an abdominal supravaginal hysterectomy had been performed 12 years previously. Examination revealed a large cystocele and prolapse of the cervix. Posterior to the cervix was an enterocele. There was a small rectocele. Operation was as follows:

An inverted T incision was made just above the external os and carried up to the urethra. The vaginal mucosa and fascia were bluntly dissected off the bladder and superiorly and laterally to the pubis. The bladder was then stripped off the remnants of the cervix until the peritoneum was visible. The cross arm of the inverted T incision was extended posteriorly to complete the denudation of the cervical cuff. The cervix was then divided anteriorly in a longitudinal direction up to the peritoneum. At the top of this incision the cervix was split by a transverse incision through the anterior lip, thus transforming the cervical cuff into a flat rectangle. (If the endocervix is functioning it should be removed.) This flap was then sutured to the subpubic fascia after the bladder had been pushed back into the pelvis. The *posterior vaginal mucosa* was then dissected further posteriorly. The uterosacral ligaments were sutured together without opening the peritoneum of the posterior cul-de-sac, and then

sutured to the superior margin of the transposed cervical flap. The outer layer of mucosa was then shaved off the anterior vaginal flaps, and the flaps were divided so as to obtain 2 strips of tissue (one left and one right), about $\frac{3}{4}$ inch wide, maintaining its integrity above. The right strip was then crossed over the transplanted cervical flap and sutured to the subpubic fascia. The left strip was then carried similarly to the right subpubic fascia. Thus, a sling was created under the transposed cervical flap. The excess vaginal mucosa was trimmed off and sutured together from below the urethra down to the point where the top of the plication of the uterosacral ligaments had been started. The posterior vaginal mucosa was then trimmed and sutured to the bottom edges of the anterior layer. A high perineal repair was then completed in the usual manner.

Examination of the patient on discharge revealed a well-healed perineum. The vagina admitted 2 fingers and was patent for about 3 inches. The anterior vaginal wall was healed, and there was no bulge on straining. There was no bulge or relaxation at the vaginal dome. Re-examination 6 months later revealed no change.

(No illustrations accompany this paper, so that it maybe rather difficult for the reader to visualize the steps of this operation, although these are quoted very fully in the abstract. Certainly it should rarely be necessary for the gynecologist to resort to the various operations which have been devised to suspend the prolapsed cervix to the abdominal wall. A cardinal rule in the treatment of prolapsed organs, it seems to me, is that they should be supported from below, and not suspended from above. Even when the body of the uterus has been removed, the cervical stump is generally long enough to permit of pretty nearly as good an application of the Manchester procedure and that of ligamentous approximation as if the whole organ is present.

As a matter of fact, I have seen a good many cases in which it has been possible to secure excellent results by the vaginal route even though there has been complete inversion of the vagina following total hysterectomy. The procedure is likely to be more difficult, as it is not always easy to outline the cardinal and uterosacral ligaments, and it may involve considerable narrowing of the upper vagina, but in other cases the procedure is much simpler, with satisfactory functional results. I would much prefer to do this than the Leport operation unless the woman is quite old or in poor general condition. The procedure of utilizing the split cervix, as recommended by Rose, may possibly be of additional help in the occasional case, although in itself it would be of little value unless combined with proper ligamentary and fascial approximation.—Ed.)

VAGINAL HYSTERECTOMY

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The author submits a preliminary review of 1,000 personally operated cases of vaginal hysterectomy. Over the same period 796 abdominal hysterectomies were performed.

Three important steps in operation which are stressed are: (1) Delivery of the fundus uteri through a cul-de-sac opening permits accessibility to clamping the lateral uterine supporting structures. (2) By inserting 2 fingers behind the uterine fundus, the bladder is elevated to prevent danger of incising the bladder wall when the peritoneal cavity is opened anteriorly. (3) A normally deep vagina requires severing the mucous membrane well down on the cervix. A slightly lax anterior vaginal wall is preferable to a tense one. The author prefers to maintain anterior wall depth by trussing the lower margin of the vesicocervical tissues to a high position by suturing to a central stump previously formed by the approximation of the uterine ends of the infundibulopelvic ligaments. A detailed description of the operative technic is included in this paper.

Of the 1,000 patients, 522 were between 30 and 60 years of age; the youngest was 22, the oldest 84. The commonest symptoms were bladder irritability, low backache, low abdominal discomfort, bearing-down discomfort and vaginal discharge. The commonest indications for operating were: prolapse of uterus, 410; second and third degree prolapse, 264; rectocele and cystocele, 473; myoma uteri, 386; metrorrhagia, 255. Malignancies of the fundus and cervix were the indication in 17 and 9, respectively. Among the preoperative findings which added to indications for operation were 23 cases of pelvic inflammatory disease.

The following operations were included in the 1,000 vaginal hysterectomies:

Cystocele repair	616
Perineorrhaphy	967
Salpingectomy	97
Salpingo-oophorectomy	90
Vaginal appendectomy	9
Cul-de-sac hernia	15
Urethral caruncle	6
Rectovaginal fistula	1
Bartholin duct cysts	5
Vaginal cyst	2
Hemorrhoidectomy	29

Immediately following vaginal hysterectomy, the abdomen was opened in 24 cases. The pathologic diagnoses, in part, were:

Myoma uteri	218
Endometrial polyps	53
Endometrial hyperplasia	84
Cystic endometrial hyperplasia	28
Adenocarcinoma uteri	16
Adenomyosis uteri	26
Squamous cell carcinoma, cervix	11
Atrophic uterus	48

There were 13 cases of hemorrhage requiring transfusion of blood or plasma during or after operation. There were 11 cases of severe preoperative anemia. Twenty-five patients had postoperative cystitis. There were 6 cases of pyelitis, 6 of pelvic abscess, 4 of thrombophlebitis, 5 of pneumonia and one of pelvic peritonitis.

In the first 500 cases there were 6 deaths.   One was due to postoperative shock, one to pneumonia, one to pulmonary thrombosis, one to intestinal obstruction, one to peritonitis and pelvic abscess, and one to peritonitis.   In the second 500 cases there was one death.   The patient was bleeding continuously from inoperable carcinoma of the cervix and operation was performed to control bleeding.

Of the series, 544 patients have been checked personally.   Cystoceles recurred in 36 cases, rectocele in 8.   Five of these patients have been reoperated.   The malignancies in Group 1 and 2 numbered 37; of these, 31 patients were alive and well in 1947.

(A personal series of 1000 vaginal hysterectomies gives a man the right to express his opinion about the operation, and this obviously is favorable.   There is more than one good way to take out most uteri, just as there is more than one good technic for removal of the appendix or gallbladder.   The only valid criticism along these lines is that a dyed-in-the-wool vaginal hysterectomist may stick to this route even when the abdominal would offer clear advantages, just as those clinics in which the abdominal technic has become the customary one may overlook the greater ease and safety of the vaginal procedure in many cases.   All this is a trite restatement of the old dictum that the operation should be fitted to the patient and not vice versa.   The practical point is that every good gynecologist should be equally proficient in both methods, although he will quite naturally, because of the training and the personal experience he has had, be partial to one or the other of the methods.

The results reported by the author, with only 7 deaths from all causes in the 1000 cases, are very creditable.   The 1 death which occurred in the second 500 cases makes one wonder why a vaginal hysterectomy was chosen as the best plan to control bleeding from an inoperable carcinoma of the cervix.   If, as I suppose was the case, there was extensive infiltration of the vagina and parametrium, it must have been a forbidding and heroic procedure which few of us would wish to tackle if the bleeding could possibly have been controlled by such safer methods as thorough curetting of the necrotic cancer tissue, the cautery and the pack.—Ed.)

STERILITY

WHAT DO WE KNOW ABOUT STERILITY?

L. W. MASON

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Between the theories which we hold relative to female sex physiology and their clinical application there is a wide breach and diversity of opinion. May some of the theories be wrong, or may we not know how to apply them properly, or is the breach chiefly due to the fact that we do not yet have therapeutic agents in the endocrine field which will do to the patient the same things that endocrines from the patient's glands will do? Particularly is the last possibility applicable to the endocrine preparations of, or related to, the pituitary.

In performing a sterility study, both husband and wife should have a good general physical examination and for the sake of their general health, any pathology found ought to be corrected. However, just how much the correction of such factors, apart from those specifically connected with the reproductive tracts of either partner, has to do with the problem of their sterility, the author is not certain. Indeed, he often has marveled at the amount of pathology frequently found in the female reproductive tract when the patient has come to him, not for a sterility study, but for contraceptive advice.

What of those cases which we complete and do not find any cause for the sterility? Certainly something is wrong, or conception would have occurred. To the writer, this simply means that at the present time we are not wise enough to find out what it is.

If we understood all the factors involved in one case where conception has occurred after many years of a barren marriage, we would have progressed a long way toward an understanding of the problems of sterility which we do not now understand.

The next class for consideration embraces those cases in which we find departures from what is considered normal. Setting aside for a moment those cases, both male and female, in whom gross pathology is found, just what specifically can be done for these others? If an endometrial biopsy shows a deficiency of estrogens or progesterone, what can we actually do about it? According to theory, these deficiencies indicate deficient ovarian function. This being the case, are there any indications for the administration of estrogens or progesterone? If there is this evident deficiency in function of the follicle and corpus luteum, should not one also assume that there is a deficiency in the primary source of the follicle, the ovum itself? If so, no secondary stimulation of the endometrium will accomplish much. The author has hundreds of endometrial slides

taken in consecutive menstrual cycles after the administration of all the gonadotropins ever on the market, and has not a single one which shows any definite improvement which could be ascribed to their use.

What is the significance of partially closed tubes? If there is *any* opening, would it not be sufficient for thousands of sperms to get through? Rubin has maintained that the uterine tubes are something more than pipes, and for them to function normally the epithelium must be normal, and there must be normal peristalsis. Perhaps in what we designate as "partially" closed tubes, the closure is only part of the trouble, a more fundamental pathology being present. And yet, all have had the experience of having patients in whom conception occurred within a relatively short time after tubal insufflation. Has the tubal insufflation been causal, or has the sequence been merely coincidental?

Do some women, or any women, have regular, normal menstrual periods without ovulation? In patients having a normal menstrual history, the author has never obtained a menstrual endometrium which showed absolutely no evidence of corpus luteum influence. It is his opinion that normal menstrual cycles presuppose a normal ovarian cycle, even though evidences of deficiencies may appear.

Does a summation of minor abnormalities in the male or female, or both, so reduce the fertility level of the couple that conception becomes impossible? If this is so, how does one reconcile it with the fact, as so often is observed, that in cases of long-standing, severe illness accompanied by marked toxemias in men as well as in women, the one physiologic function which seems to remain unimpaired the longest is the function of reproduction? The writer has delivered a patient 4 times who is constantly toxic from a severe bronchiectasis. It does not seem that one, or half a dozen, minor, or moderately major physical defects not related directly to the reproductive apparatus can result in long continued sterility.

Just how inimical are "inimical" cervical and prostatic and seminal vesicle secretions? No matter what the pathology of the prostate or seminal vesicles, it seems that they could have no direct effect in producing a diminished number of sperms, which is the function of the testicle. In the author's experience, cases of impaired vitality of sperm are not usually connected with visible evidence of infection in these organs.

In general, practically all of the factors involved in sterility, other than such mechanical factors as tubal closure, involve fundamental deficiencies in the ovary or of spermatogenesis. In the writer's opinion, many of the present problems will be solved when we have a pituitary hormone which is really physiologic in action. The present state of our lack of knowledge should serve as a stimulus toward redoubling our efforts to work out these problems.

(Everyone who treats many cases of sterility has asked himself many of the questions which worry the author of this paper, and yet there are few who would take as extremely a pessimistic attitude toward the problem as he does. Most of them, I suspect, are at least moderately gratified at the percentage of successes which do seem referable to the diagnostic and therapeutic measures employed. This is said with full appreciation of the fact that the

gynecologist unquestionably often gets credit for pregnancies which follow treatment, but to which the latter made no real contribution. Incidentally, he would be less than human if he accented very strongly to the patient his doubts as to his particular contribution in these 3-way pregnancies, requiring the services of the wife, the husband and the doctor. I can easily see that this innocent statement will be seized upon by some of my more ribald readers.

And yet, in the case of women sterile for many years, it is difficult to scoff at the not infrequent successes following tubal insufflation, thyroid medication of wife or husband or both, and any of the numberless other therapeutic measures so often indicated.

When the author expresses skepticism about the anovulatory cases, those of male infertility, the essential worthlessness of such pituitary gonadotrophes, and various other aspects of the problem, he is on safer ground, and will have lots of company in his views. Incidentally, I was surprised to see his statement that he "has never obtained a menstrual endometrium which showed absolutely no evidence of corpus luteum influence." I have seen many such instances both in the immediately premenstrual phase or after the beginning of bleeding, and I believe that this is the usual experience, although there are wide variations in the incidence of anovulatory cycles as reported by different authors.—Ed.)

CAUSES AND TREATMENT OF TUBAL OCCLUSION

L. Snaith

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Estimates of the incidence of all degrees of tubal occlusion vary between 18 and 50 per cent of all cases of sterility. The findings discussed in this paper are based on a survey of approximately 800 sterile marriages. In 60 patients complete occlusion of the Fallopian tubes was found to be present and in many other women definite defects in tubal function, without complete occlusion, undoubtedly contributed to the infertility.

The etiology of occlusion is discussed. Primary tubal occlusion is commonly associated with genital hypoplasia. The writer has diagnosed genital hypoplasia in about 28 per cent of all types of tubal occlusion. Secondary tubal occlusion is, of course, usually associated with inflammation which may be tuberculous, puerperal or gonococcal. Partial or complete occlusion may also be produced by tumors, especially cornual adenomyomata, but elongation or compression of the tubes may be produced by parauterine cysts or fibroids. Involvement of the fimbrial end of the tube in a mass of adhesions between ovary, broad ligament and lateral pelvic wall is not uncommonly found in cases with no history to suggest infection. Some of these cases are due to endometriosis, but in others it would appear that there has been hemorrhage into and around a corpus luteum or follicular cyst. Apparent occlusion may occur as a result of premenstrual endometrial swelling in the cornual region.

First among diagnostic means must come Rubin's test. It is of value as a

therapeutic measure as well as being a diagnostic necessity. It has the advantage over other methods of tubal investigation in that it may be combined with endometrial biopsy. X-ray visualization of the tubes, or hysterosalpingography, has a rather different diagnostic function, and is particularly applicable to cases apparently occluded to insufflation or where the past history suggests that occlusion will be present.

Methods of treatment of tubal occlusion fall into 3 groups: medical measures, chiefly hormonal, attempts at overcoming obstruction by insufflation or lipiodol and, in a small group of cases, major surgical procedures. In discussing the therapeutic value of insufflation, the writer calls to mind the effects of chance and lapse of time in playing a part in the cure of many sterile marriages. Most writers on infertility suggest that insufflation or lipiodol-injection, in the absence of demonstrable pelvic pathology, is followed by pregnancy in a high proportion of cases. Although 28 per cent of the writer's "cures" followed soon after one or more insufflations or lipiodol tests, of all women in whom insufflation was carried out only 30 per cent became pregnant, and the incidence of success in the series treated, solely as a result of insufflation or lipiodol injection, cannot be more than 10 per cent.

Since Clauberg demonstrated, in 1938, that non-patency of the Fallopian tubes might be overcome by estrogen therapy, much attention has been given this form of treatment. Some cases of success may be due to improvement in tubal spasm rather than to the development of hypoplastic tubes, but this possibility in no way invalidates a trial of hormone therapy when occlusion has been found. In 30 of the writer's own "sterility cures" in which partial or complete tubal occlusion was present, there is evidence that success could be attributed to hormone therapy in 11 cases, 8.5 per cent of all "cures." Patency has been achieved, apparently by hormones, in other cases of occlusion, although pregnancy has not occurred to date.

That obstruction due to tumors may be overcome by abdominal operation is doubted by none, but where disease lies in the tube itself the outlook appears to be regarded as unsatisfactory, though numerous plastic operations have been devised. When the occlusion is fimbrial, the prospect of surgical success seems greater and the possibility of ectopic pregnancy less.

For the past 5 years at Newcastle General Hospital, salpingostomy has been carried out with the aid of amnion prepared by the Department of Neurosurgery, where it is used to prevent intracranial adhesions. The amnion is obtained from cases of cesarean section. It is friable and its proper application to the tube demands the use of very fine interrupted catgut sutures, considerable patience and a careful selection of case and planning of the shape of pieces of amnion to be used. Cases with fimbrial end occlusion are most hopeful, and those with thickened rigid tubes are usually rejected. Amnion has been used in 21 cases; in most there was complete tubal occlusion. Of the 21 cases, 14 have been followed up by lipiodol. In 13 of these full patency was demonstrated; in the remaining one only slight escape of lipiodol occurred. Only 2 pregnancies are known to have occurred among these cases, but several were dealt with only recently.

In conclusion, in a series of 800 cases of infertility, tubal occlusion is known to have been present in 130 and has been suspected in many others. Of these, 60 patients had complete occlusion. Pregnancy has occurred in 30 cases where there was evidence of significant tubal occlusion; hormones played an important part in the treatment of 11 of these, and 3 were subjected to major surgery. Twenty women became pregnant after insufflation or lipiodol, combined with hormone therapy in some cases. Of all cases of sterility, 28 per cent of the successful cures followed insufflation or lipiodol, though it is not certain that this procedure was responsible for success in all these cases. 11 figures.

(This paper presents an excellent discussion of tubal occlusion and the important role it plays in such a large proportion of sterility problems. For practical purposes the "primary tubal occlusion" due to genital hypoplasia, as described by the author, can, I believe, be almost disregarded. The author expresses my own sentiments with regard to the greater diagnostic and therapeutic value of the Rubin procedure over other methods of tubal investigation, with full appreciation of the fact that salpingography may in some cases be of supplementary value, and that in some clinics it is practically a routine procedure. The pros and cons of this subject have been commented on in these pages at various times in the past.

I would not personally list as one of the advantages of tubal insufflation that it can be done at the same time as endometrial biopsy. Most of us prefer to do insufflation in the preovulatory phase, and I ordinarily like to carry it out on about the 9th day of the cycle, shortly before the usual optimum fertilization span for most women, in order theoretically to take full advantage of the possible therapeutic effects of the insufflation. While insufflation can be done in the postovulatory phase, it carries with it the hazard of blowing out the already extruded and possibly fertilized ovum. Moreover, a marked premenstrual swelling of the uterine mucosa may lead to wrong conclusions as to the patency of the tube.

The value of endometrial biopsy in the interpretation of the hormonal response of the uterine mucosa, and especially as to whether or not ovulation has occurred, becomes progressively greater the closer it is done to the approaching period. If it is performed shortly after ovulation it is much more difficult to interpret the endometrial findings on the above points. For such reasons as this I believe that we can get the full value of both insufflation and biopsy only by doing them separately and at those phases best suited for each of them.

It is true that the pathologic physiology as well as the pathologic anatomy of the tube must be reckoned with in cases of sterility, but it must not be forgotten that the former is the result of the latter. Just how much this physiologic factor can be helped by hormone therapy I do not know, nor can this factor be accurately determined by the results, or the assumed results, of such therapy, although it is recommended by most students of the subject, including Rubin himself. My own experience with it has not been impressive or convincing to me, although I have no criticism to make of its use or of a certain measure of rationale in such therapy.

As for operations to restore tubal patency, the author exhibits the lack of enthusiasm which is shared by practically all of us, although there is certainly a small proportion of cases in which such attempts are fully justified, with full and honest explanation to the patient as to the slimness of her chances for success. All sorts of methods have been suggested to maintain the patency of the lumen in such cases, especially in those where the indicated procedure has been salpingostomy. The author's employment of amnion is of interest, especially as this same tissue has been used by others for somewhat similar indications. For example, Burger of Budapest, now at Wurzburg, utilized amniotic membrane to facilitate the epithelialization of the artificial vaginal canal in cases of congenital absence of the vagina. My own plan in cases of plastic tubal operations has been to leave a double

loop of No. 2 chromic catgut in the lumen, anchoring it in the tubal wall well away from the new lumen, in the hope that epithelialization would be completed around the catgut before absorption of the latter.—Ed.)

METHODS OF INCREASING FERTILITY IN DOMESTIC ANIMALS

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In this discussion on increasing the fertility of cattle, the writer states that more attention should be given to the nutrition of males and females, with special emphasis on vitamin A. The use of hormonal substances, notably estrogens, chorionic gonadotropes and testosterone, have value in selected cases. Cystic degeneration of the follicles in cattle may be overcome by early treatment with the gonadotropic substances. Increasing the energy of sperm by various means may prove valuable. 2 figures.

MISCELLANEOUS

CONGENITAL ANOMALIES OF THE FEMALE REPRODUCTIVE ORGANS

EMIL NOVAK

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The writer sketches very briefly the factors concerned in congenital anomalies of the female sex apparatus. Various portions of the apparatus may be completely lacking (aplasia), or they may fail to develop beyond the most primitive stages (agenesis), there may be duplication of various segments, or there may be partial or complete failure of fusion of the 2 müllerian canals. Other possible anomalies may affect the lower vagina and external genitalia, these involving chiefly the derivatives of the urogenital sinus, and often being associated with anomalies of the müllerian segment.

One should always bear in mind that such genital anomalies often are associated with congenital anomalies of the urinary tract; therefore, urography should be a routine part of examination of all such patients.

With any of these anomalies, the general body development and psyche of the patient may be typically feminine. In a smaller group of cases, anomalies of the sex apparatus are only a part of a more profound genetic disturbance involving chromosomal factors.

It is easily possible, in some of the lower forms, to disturb and even invert the genetic sex balance of the embryo, and similar disturbances undoubtedly occur in the human. The earlier the extrinsic factors become operative in embryological development, the more profound the resulting sex changes. Thus are brought about the various forms of true and pseudo-hermaphroditism.

Probably the most commonly encountered anomalies in practice are congenital absence of the vagina, imperforate hymen, the fusion failures of the müllerian ducts, and hermaphroditism, true and false.

The Baldwin operation for creating a vaginal canal is no longer justifiable because of its magnitude and real hazard. Probably the most satisfactory method in most cases is that of Wharton, either with or without Thiersch grafts.

Most fusion anomalies of the müllerian duct involve the uterine segment, producing all the well known variations. In only a minority of cases does the condition *per se* call for treatment, but the complications to which it gives rise often do, such as ectopic pregnancy arising in a rudimentary horn, or the obstetric problem of blockage of the birth canal by the nonpregnant half of the double uterus.

True hermaphroditism is very rare; Young's compilation (1937) revealed only

9 genuine cases, with only a small group since then. The much more common pseudo-hermaphrodites are designated as male or female according to the testicular or ovarian character of the gonad. This is usually based on biopsy of the latter. All sorts of combinations of male or female gonads with accessory sex organs of either sex may be encountered.

A few cardinal principles in the treatment of pseudohermaphroditism are mentioned. First and, in the author's opinion, most important is that the sex nature of the gonad plays a relatively unimportant part in deciding the sex to which the patient shall be assigned at operation. Almost never should an adult patient be taken out of the sex category in which she was raised, because of the psychological upheaval that would follow. Secondly, it should be remembered that the secondary sex abnormalities may often be the same whether the gonads are ovaries or testes. It is probably better to conserve one or both gonads, for they probably exert no "contaminating" influence on the patient's life. Finally, the psychological management of such patients is of great importance. They cannot be treated simply as interesting biological and surgical problems, but as unfortunate humans with sick and tortured minds as well as malformed bodies

BACK PAIN FROM THE GYNECOLOGICAL STANDPOINT

E. B. KING

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The writer discusses various pelvic conditions in regard to possible association with back pain in women. It is generally recognized that abnormalities in position of the pelvic organs very rarely will give rise to backache. An otherwise normal uterus in retroposition practically never causes backache. It is infrequent for patients with marked relaxation of the vaginal introitus to have backache as the presenting symptom. Again, it is rare to have backache as the chief complaint in the presence of a prolapsed ovary.

If the pelvic pathology is such that congestion or edema of the tissues has occurred, or if there are adhesions within the pelvis, there is more apt to be a cause-and-effect relationship than if these conditions are lacking. Chronic cervicitis not infrequently is responsible for an associated inflammatory reaction in the pelvic lymphatics, particularly along the course of the uterosacral ligaments. When the latter condition is present, the patient not infrequently presents back pain as a predominant symptom. In cases of acute or chronic inflammatory involvement of the upper generative tract, backache is not uncommonly one of the complaints, but it is rarely the chief complaint. It is surprising how rarely back pain can be definitely ascribed to the presence of even quite large pelvic tumors and cysts. In cases of endometriosis in which the posterior surface of the

uterus and cul-de-sac are involved to a considerable degree, back pain may be a predominant symptom. If the endometriosis is limited to the ovary alone, sacral pain is practically never an important feature. Back pain may be associated with premenstrual tension, in which case treatment is directed at this syndrome.

It is a difficult decision to reach when we wish to ascribe the back pain to a psychogenic state. Certainly, every organic cause must be ruled out. These patients not uncommonly will complain of being "tired all over," or of extreme nervousness or tension. By keeping in mind that back pain due to organic disease is often prolonged by psychogenic causes, and by asking for psychiatric help when indicated, we can relieve many of these chronic invalids.

The writer concludes by saying that the association between the symptom of back pain and actual pelvic pathology is difficult to evaluate. By doing a complete physical examination—not only a pelvic examination—and by obtaining a careful history, one's clinical results may be considerably improved. One should not overlook the possibility of an associated orthopedic, urological or neurological condition which might be the real cause for the patient's complaint. A guarded prognosis will result in fewer disappointments.

(This is a very sensible review of an exceedingly common problem in gynecological practice. The first paragraph of the abstract should be underscored for the benefit of the numerous practitioners who seem to have the idea that low backache is generally indicative of some gynecological condition, usually a displacement of the uterus. Such patients are thus referred to gynecologists, swelling our practices very materially, but adding to our diagnostic problems.

While it is of course true that in a minority of cases backache is actually produced by pelvic diseases, some of which the author has discussed, the great majority of them, in my experience, have been due to trouble in the back itself. This statement does not of course refer only to structural changes in the back, like arthritis, displaced disks, curvatures, etc., but even more frequently to postural, musculo-ligamentous or even psychogenic factors. In more troublesome cases we are apt to "pass the buck" to the orthopedist, and all too often the patient's backache becomes a headache to the orthopedist.—Ed.)

DYSPAREUNIA: A PROBLEM FOR THE GENERAL PRACTITIONER

R. T. FRANK

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Dyspareunia in a series of 349 patients represented an incidence of about 1.5 per cent of gynecologic private patients seen over a period of years. Of the 349 patients, 29.6 per cent complained solely of dyspareunia, 47.7 per cent gave it as the main complaint and 22.7 per cent mentioned it incidentally. Of the entire group, 55.3 per cent had never conceived. In 30 per cent the dyspareunia

had existed since marriage. The duration in the entire series varied from honeymoon (one to 60 days) to 10 years or more. The site of the pain was introital in 60 per cent, deep in 29 per cent, both superficial and deep in 10 per cent, and not ascertained in 5 patients.

Symptoms which developed with marriage were termed primary; when the onset occurred later they were called secondary. Primary introital dyspareunia most commonly developed as a consequence of coital trauma, local infection and leukorrheal irritation (including Trichomonas). In 7 cases, congenital vaginal septums were at fault. Absence of the vagina is not discussed. Secondary introital dyspareunia (20 per cent) resulted from menopausal shrinking, too tight plastic or episiotomy repair or kraurosis. Deep dyspareunia arose from retroflexion with prolapsed ovaries, deep pelvic inflammations, parametritis, exudates, adnexitis and endometriosis.

Localizable symptoms required local treatment in addition to psychic suggestion. Lesions acquired during the honeymoon are treated by interdiction of intercourse, hot sitz baths and, if the vulva is painful and swollen, wet dressing of 0.5 per cent aluminum acetate. If pronounced spasm, vaginismus or anxiety has already appeared, after healing is complete, the tube treatment (discussed later is this paper) should be used for 2 weeks before resumption of intercourse. Inflammations should be treated along orthodox lines. Congenital septums require surgical excision. In mild cases of menopausal dryness and mucosal shrinkage, lubrication may be sufficient to relieve. When pronounced senile changes are noted, occasional 12-day courses of estrogenic vaginal pessaries prove helpful. In cases of too tight plastic repair or episiotomies, lubrication and more dorsal intromission relieved some. In a number, a reverse plastic operation was required. In the one case of kraurosis encountered by the writer, vulvectomy was performed.

Endometriosis and pelvic inflammation causing dyspareunia require treatment of the underlying condition. The author has never operated on retroflexion for dyspareunia per se. The knee-chest position is prescribed and later an appropriate pessary is inserted.

Normal pelves were noted in 63 patients (17.5 per cent). Of these, neuroses and psychoneuroses existed in 54.8 per cent, contrasting with those patients in whom recognizable pelvic lesions were found and who showed only half as many nervous symptoms (24.6 per cent). In psychogenic dyspareunia the initial local or general factors may disappear, leaving no trace of any initial local causation (64 per cent); in the remainder some inciting local cause was still determinable. When dyspareunia is based on nonlocal causes or when local complaints are far overshadowed by nervous symptoms, it indicates a defense mechanism developed by the patient. The defense may be directed against sex and physical congress in general, fear of pregnancy, or aversion to the partner. The duration of the neuroses in the 63 patients ranged from one month to 14 years, with an average of 2 years.

The husband problem predominated in 36 cases and was most probably an important factor in many more. In a number of instances a genitourinary specialist to whom these husbands were referred was able to help them.

The author has developed a simple technic which has rarely failed in patients who wanted to be cured. The attitude of the patient, therefore, must be explored carefully and minutely at the outset. If necessary, vaginal examination is eliminated at the first visit. Coitus is forbidden, and hot sitz baths, sedation and twin beds are ordered.

At the next visit, 5 to 7 days later, the improvement in "entente" will be great. A short separate interview with the husband, who has been invited but too often fails to attend, will enlighten him and enlist his full cooperation.

Local examination (one finger vaginally, small speculum) shows entire absence of local lesions and causes, but may arouse spasm even though no pain is elicited by the deliberate gentleness. With the patient still in the lithotomy position, the writer then produces with emphasis 2 pyrex test tubes, one ⅝ inch, the other one inch in diameter. The patient is instructed for the first week to insert the smaller tube, well lubricated, twice daily for 10 minutes. The patient's position should be dorsal, the thighs drawn up and separated, the introduction deep, and this maneuver should be repeated at least 3 times at each session. The larger sized tube is used during the second week. The patient then herself introduces the tube under supervision, and if necessary is repeatedly instructed and encouraged. She is assured convincingly that at the end of this period coitus will not only cause no pain but may prove pleasurable. The result has been almost 100 per cent cures except in the few in whom a deep-seated psychic basis exists. The method will not cure phobias, it will not make a disliked husband attractive, but it will make coition physically painless and, when no deep-rooted prejudices exist, responsiveness may develop.

In conclusion, in psychogenic dyspareunia great caution must be exercised in attempting to treat dyspareunia of long duration. The attitude of the patient is decisive; only those who manifestly wish to be cured should be treated. Those in whom the defense and resistance complexes predominate should be left undisturbed and if possible referred to a competent psychiatrist for preliminary treatment.

(This is a very comprehensive study of an important and frequently encountered problem, the treatment of which usually calls upon those psychosomatic resources which must form a part of every gynecologist's armamentarium. The author discusses all the many possible causes of this disorder. Even in those cases in which some perhaps obvious physical cause is present, it is rare that the psychic factor is not superimposed. The coital trauma and resulting pain of the honeymoon may leave such an impression upon the patient's psyche that even after any mechanical or traumatic factor has disappeared, the mere approach of the husband may induce vaginal spasm and a continuance of the coital difficulty. As a matter of fact, one of the most important points to stress in the premarital instruction of prospective young husbands is gentleness and consideration for the wife.

Trichomonas vaginitis is among the commonly observed causes of secondary or acquired dyspareunia, and I have seen a good many instances in which tender episiotomy scars, especially after poor repair, were responsible. In the same way, poorly done perineorrhaphy, with over-approximation of the levators or the more superficial tissues, may produce dyspareunia, and in this type colpoplastic procedures are not infrequently indicated for correction of the difficulty.

It should not be forgotten that dyspareunia is not infrequently a defense mechanism built up by the wife who no longer loves her husband or in whom the latter engenders a

feeling of revulsion. Almost always a really complete examination, envisaging the psycho-somatic as well as the purely physical factors, will throw light on the underlying cause and point the way to proper treatment. Gentleness on the part of the physician in his examination, together with a sympathetic attitude toward the patient's problem, are of obvious importance if one expects her full cooperation.—Ed.)

BACKACHE IN WOMEN

H. H. Fouracre Barns

Practitioner, **160**: 68–70, 1948

This writer attempts to show that pelvic lesions may produce backache in the lumbo-sacral area by causing an increase in tension in the posterior segment of the pelvic floor. It must be emphasized, however, that such lesions may exist without producing such an increase in tension and in such cases are not the cause of the accompanying backache. It is the lack of appreciation of this fact that accounts for so many patients having their backache attributed to a pelvic lesion whereas it is in fact due to an undiagnosed orthopedic cause. In order to treat the woman with this symptom, it must first be determined which of the many causes is responsible for the backache in the given case. This requires full examination of the spine, including x-ray, and of the pelvis, and very often the help of the orthopedic surgeon or physiotherapist.

(In the great majority of cases of backache the cause of the backache is in the back. To say that it cannot be produced by pelvic pathology would of course be foolish. It can, for example, certainly be caused by at least some of the marked retroflexions, more especially those of acquired type, associated with subinvolution or congestion. It can also be due to the presence of large pressure-producing tumors, as well as other causes. But none of these should be considered culpable until other local factors in the back receive proper consideration. The average lay woman who suffers with persistent backache is apt to wonder if she has kidney trouble if the backache is in the lumbar region, often because she is familiar with the picture of the poor suffering woman holding her hand over her back in the widespread advertisements of Doan's Kidney Pills. If her backache is low down, she suspects that she has some sort of female trouble. The doctor's job, therefore, is often the very valuable one of reassurance after the proper kind of examination. Even when, as will be true in the majority of cases, he feels sure that the backache is of musculo-ligamentous or postural type, the therapeutic problem is not always an easy one. If such simple measures as proper support, rest periods and the local use of heat in some form do not give relief, he will probably wish the collaboration of the orthopedist in the further management of the problem. Finally, it must not be forgotten that lesions of more serious type, such as displaced intervertebral discs, spinal arthritis, kidney stones and a variety of other conditions may be responsible in some cases, the moral being that no case should be treated too casually and without proper study.—Ed.)

RECENT IDEAS IN GYNECOLOGY

J. T. SMITH

Tufts Medical School and Joseph H. Pratt Diagnostic Hospital

The writer refers to the work of Papanicolaou, Meigs and Ayre on the use of the vaginal smear in cancer diagnosis. The method of obtaining and preparing the smear is briefly discussed. That the cancer cells may vary tremendously is pointed out. Types of cells not regularly found in normal smears which must be differentiated from cancer are described.

Where there is no clinical evidence of cancer, it is believed that the smear test has great value as a quick, relatively inexpensive and painless method for screening women. It is believed that when cancer does exist, cells are present in the smears. The problem is to train people to recognize them. No patient should, at present, be advised to undergo operation or serious treatment for cancer on the basis of this test alone. What the test can do is pick out the patient for whom a diagnostic curettage or biopsy is a "must."

Some such method of making an early diagnosis of cancer is, at present, the only prospect for reducing the mortality from this disease. How important early diagnosis is, is illustrated by TeLinde's study of carcinoma in situ. Among many hysterectomies, 16 of these very early noninvasive islands of malignant change were found. The average age of these 16 patients was about 12 years younger than the average age of all patients with obviously invasive cancer. In other words, on the average there appears to be a period of a decade or so during which the malignancy is entirely contained by the defensive mechanisms of the body, when the tumor is absolutely localized and quite curable by surgery or radiation. The vaginal smear should help to diagnose the trouble during this early period of opportunity.

In connection with the radiation treatment of uterine cancer, it is mentioned that the cervical smear is of great value in estimating the results of treatment. A vaginal smear taken 7 or 10 days after radiation shows great swelling of the cancer cells, with utter dispersion of the nuclei. If the cells look unchanged, we know that the tumor has been unaffected by treatment, that it is radiation-resistant, and that much increased dosage, or surgery, must be employed.

(See comment on preceding abstracts of papers by Posey and Cunningham, and Scheffey, Rakoff and Hoffman.—Ed.)

Announcement

The Editors are pleased to announce that

the next (October) issue of the

Obstetrical and Gynecological Survey

will be devoted to the

PROCEEDINGS OF THE CONFERENCE

ON NORMAL AND PATHOLOGICAL

PHYSIOLOGY OF PREGNANCY

held at the Hotel Pennsylvania, New York,

January 30 and 31st, 1948

under the sponsorship of

THE COMMITTEE ON

HUMAN REPRODUCTION

of the NATIONAL RESEARCH COUNCIL

in behalf of the

NATIONAL COMMITTEE

ON MATERNAL HEALTH

AUTHOR INDEX
AUGUST, 1948

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FOREWORD

For a number of years the National Committee on Maternal Health has sponsored annual conferences in New York City dealing with various aspects of human reproduction. Founded in 1923 by Dr. Robert L. Dickinson and a group of progressive physicians, this organization has a distinguished record of achievement through the many fundamental studies of the reproductive process it has fostered and supported. Its annual conferences have been characterized not only by the original and informative character of the papers presented but, to an unusual degree, by the outspoken and searching nature of the discussions which followed.

In 1947, as the result of certain organizational changes, the scientific activities of the National Committee on Maternal Health were transferred to a newly founded Committee on Human Reproduction of the National Research Council. The fiscal functions are retained by the National Committee on Maternal Health, now a lay body. Hence, the most recent conference of the National Committee on Maternal Health, held in New York City on January 30 and 31, 1948, appears over the name of the Committee on Human Reproduction of the National Research Council. The proceedings of this conference are presented in this issue of the *Obstetrical and Gynecological Survey*. Two papers which were on the program of the Conference are not included in the group, being omitted at the request of the authors, namely the contributions of Dr. Willard Allen, Professor of Obstetrics and Gynecology, Washington University, St. Louis, and Dr. J. S. L. Browne, Director of the Royal Victoria Hospital, Montreal, Canada.

EDITORS

THE NORMAL
AND PATHOLOGICAL PHYSIOLOGY
OF PREGNANCY

Proceedings of Conference of Committee on Human Reproduction
of the National Research Council

IN BEHALF OF

THE NATIONAL COMMITTEE ON MATERNAL HEALTH
Hotel Pennsylvania, New York, N. Y.
January 30 and 31, 1948

Introductory Statement by Conference Chairman,
DR. EARL T. ENGLE

The Committee on Human Reproduction of the National Research Council presents the Proceedings of the Conference on the Normal and Pathological Physiology of Pregnancy, which was held in New York City January 30 and 31, 1948.

This conference, sponsored by the Committee on Human Reproduction, is a direct lineal descendent of the annual Conferences presented under the auspices of the National Committee on Maternal Health.

It is the aim of this Committee to support fundamental research in the many technical aspects of problems of human reproduction. This series of conferences has attempted to point out the areas where intensive research is needed by summarizing and correlating existing knowledge.

It is to be hoped that the contributions presented herewith will activate further research in the basic physiology of pregnancy, thereby directly benefiting those concerned with the disturbed physiology of the pregnant woman.

The Committee wishes to thank each of the contributors who have given so freely of their time and knowledge and each of the distinguished chairmen who conducted their respective sessions.

Morning Session, Friday, January 30, 1948
Dr. Arthur T. Hertig Presiding

SOME FUNCTIONAL ACTIVITIES OF THE PLACENTAL TROPHOBLAST*

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The trophoblastic chorionic epithelium is the essential parenchyma of the placenta. It consists of the cellular and syncytial trophoblast. The cellular trophoblast comprises the trophoblastic shell and cell columns, the cell islands and the Langhans cells of the chorionic villi. The syncytial trophoblast is secondarily derived from the cellular trophoblast which it very gradually replaces. The Langhans cells differ in a number of cytological and histochemical respects from the cellular trophoblast of the trophoblastic shell, cell columns and cell islands.

It is the purpose of this communication to discuss briefly various functional activities of the trophoblast as investigated by a variety of histochemical methods applied to sections of human placenta and as studied experimentally in mouse eggs transplanted to extrauterine sites. The histochemical methods include various techniques by which nucleoproteins, mucopolysaccharides, glycogen, lipids, phosphatases and oxidases can be demonstrated in tissue sections. The material was studied with the ordinary daylight microscope as well as with the aid of polarized and ultraviolet lights.

The trophoblast, being the essential parenchyma, provides for the growth of the placenta. The cytotrophoblast represents the germinal tissue from which the syncytium is derived and it declines as the syncytium increases in amount. It is probable that the syncytium is capable of undergoing a certain degree of independent growth by amitotic division of its nuclei.

The trophoblast provides for the nutrition of the embryo by the destruction and absorption of parts of the uterine decidua and by the absorption of metabolites from the maternal blood circulating in the intervillous space. The transfer of various metabolites as well as the destruction of parts of the decidua is mediated by a variety of enzymes and chemical processes, some of which it is possible to study by histochemical means.

The trophoblast also serves as an avenue of excretion for a variety of fetal waste products.

In addition to these various functions it has become evident in recent years from endocrinological and chemical investigations that the placenta is an important endocrine organ which forms and secretes both steroid and chorionic gonadotrophic hormones. The formation of these lipid and protein bodies in-

volves complex metabolic syntheses. Experimental and histochemical methods shed some light on the probable sites of localization of these substances in the placenta.

The trophoblast is very rich in cytoplasmic ribonucleoproteins as can be demonstrated by suitable histochemical methods. The presence of a great amount of this substance in the early part of gestation suggests that the placenta is an important site of protein synthesis.

The cytotrophoblast and the syncytium play different and distinctive roles in respect to these various functional activities of the placenta.

The Production of Cytolytic Enzymes by the Trophoblast. In the first months of pregnancy the cytotrophoblast of the trophoblastic shell appears to produce proteolytic and cytolytic substances capable of attacking the endometrium. In the early stages of normal gestation in primates, hemorrhage in the decidua coincides with the erosion of the uterine mucosa by the advancing trophoblast. It has generally been assumed that the extravasated blood originates from maternal vessels whose walls are actually invaded by the trophoblast. On the other hand, there is reason to believe that a chemical substance is elaborated by the trophoblast which can initiate such changes in decidual tissue which is not yet in contact with the egg. In the macaque, evidence of such a chemical factor is found in the fact that the epithelium at the secondary implantation site begins to proliferate before erosion of the uterine surface has taken place (Wislocki and Streeter, '38). In a previllous human ovum of 11 days' ovulation age an area of congestion and hemorrhage was found in the opposite endometrial surface which had merely been in close proximity to the implantation site (Hertig and Rock, '41).

Similar proteolytic activity has been demonstrated experimentally in the presence of fertilized mouse ova transplanted to various extrauterine sites including the anterior chamber of the eye (Runner, '47; Fawcett, Wislocki and Waldo, '47). In the eye of a mouse containing a proliferating ovum, leakage of blood from engorged vessels in the iris and cornea appears to take place before a blastocyst has actually become attached to the wall of the anterior chamber. It is noteworthy also that blood begins to accumulate behind the iris at the same time that it appears in the anterior chamber. Inasmuch as the vessels on the back of the iris and ciliary body are not in contact with the blastocyst and hence are not apt to have been disrupted by actual invasion, the most satisfactory way to account for the bleeding in the posterior chamber is to attribute it to a chemical product of the trophoblast. Although the trophoblast does invade maternal vessels in later stages of implantation, direct observation and study of histological sections of ova transplanted to the eye suggest that the interstitial hemorrhage and edema in the early hours of nidation are the result of diffuse damage to vessels by cytolytic enzymes emanating from the trophoblast. Further evidence of a cytolytic factor is demonstrated by the observation that ova placed in the eye are capable of developing in close proximity only until the most precocious one among them begins to implant. Thereafter the others quickly degenerate. Finally, bits of chorionic villi obtained from human placentas of the first months

of pregnancy and grown on plasma clots liquefy the medium (Gräfenberg, '09; Friedheim, '29; Caffier, '29).

The role played by the ovum in the implantation process has been investigated recently by Blandau ('47) by a different kind of experiment. He inserted glass or paraffin beads of the approximate size of blastocysts into the uterine lumina of rats and guinea pigs between the 2nd and 6th day after the onset of behaviorial estrus. The animals were killed between the 8th and 12th days after the onset of heat and their uteri were examined to determine the fate of the beads. A definite species difference was observed in the endometrial response. In the rat the formation of the decidual crypts and the implantation of the beads into them occurred in the same manner and rate as did implantation of ova in the controls. In the guinea pigs, on the other hand, the beads did not penetrate the uterine epithelium and the decidual reactions induced by their presence in the uterine lumina were minimal.

In attempting to evaluate these observed differences it should be recalled that the blastocysts of the rat normally implant at the surface in crypts of the mucosa, whereas those of the guinea pig implant interstitially by penetrating promptly beneath the surface of the mucosa. Blandau's results would seem to suggest that for the ova of the rat to implant no chemical factor was needed, whereas for the ova of the guinea pig to penetrate the endometrium a chemical agent was necessary. Since rat and mouse are otherwise very similar in their modes of implantation, one might expect their requirements to be identical. The observations cited above upon fertilized mouse eggs growing in extrauterine sites illustrate conclusively that the blastocysts of this animal liberate chemical substances which act on the maternal tissues. This suggests that, although the decidual changes in the mucosa of the rat can be elicited by a purely mechanical stimulus and proceed autonomously as found by Blandau, the eggs may nevertheless secrete a chemical substance necessary for the initiation of normal implantation and for the maintenance of the mutually dependent interactions of the trophoblast and decidua.

The Human Uterine Decidua and its Erosion by the Trophoblast. In pregnancy the human endometrium contains enlarged, actively secreting glands and characteristic decidual cells. The uterine glandular epithelium and the decidual cells are laden with glycogen and lipids. Acid phosphatase is abundantly present in the glandular epithelium and decidual cells (Wislocki and Dempsey, '48), while alkaline phosphatase is especially plentiful in the glands as well as in the endothelium of the endometrial blood vessels (Dempsey and Wislocki, '47). The decidual cells are surrounded by an argyrophil reticulum and a ground substance which is intensely metachromatic. This metachromasia is attributable to the accumulation of acid mucopolysaccharides in the stroma with the onset of gestation (Wislocki and Dempsey, '48). Metachromatic mucoprotein is also demonstrable in the lumens of the uterine glands.

The histological appearances at the margin of the growing trophoblastic shell of the human placenta suggest that the elements of the decidua are attacked and slowly destroyed by the action of the cytotrophoblast. In sections which have

been impregnated by silver, the dissolution of the reticulum fibers can be observed. Immediately adjacent to the border of the trophoblast, the fibers become broken up and the individual bits dissolve apparently in the outermost part of the matrix of the trophoblastic shell (cf. Wislocki and Bennett, '43, plate 9). Similar fragmentation of collagen fibers in the vicinity of the trophoblast has been noted in the placentas of rodents (Wislocki, Deane and Dempsey, '46, plate 10) and cat (Wislocki and Dempsey, '46a, fig. 5).

Apparently the metachromatic acid mucopolysaccharide forming the ground substance between the decidual cells is also destroyed. Like the reticulum, it ceases quite abruptly at the margin of the trophoblastic shell, no metachromasia whatsoever being noticeable in the interstitial matrix of the shell. The multiplicity of the substance dissolved by the growing cytotrophoblast suggests the release of relatively powerful proteolytic enzymes.

It is interesting to speculate on the role of the mucopolysaccharide present in the decidua. The metachromatic ground substance extends with undiminished intensity of staining right up to the border of the trophoblastic shell. This observation indicates that the trophoblast does not release an enzymatic "spreading factor," because, if it did, one would expect the decidual ground substance to be hydrolyzed with consequent diminution of its metachromasia in the immediate vicinity of the trophoblastic shell. This acid mucopolysaccharide may, therefore, represent a viscous barrier capable of retarding the activity and progress of the trophoblast. The ground substance of the human decidua is still intensely metachromatic in the second half of pregnancy at a period when, according to Caffier ('29), the trophoblast has completely lost its proteolytic activity. For this and other reasons, it appears as though the changes occurring in the fetal-maternal junctional zone of the placenta during the course of gestation are probably the outcome of both mutually supportive and mutually antagonistic forces resident in the trophoblast and in the decidual barrier.

The Production of Chorionic Gonadotrophic Hormone. It is generally accepted that this hormone is produced by the trophoblast but it is uncertain whether it originates from the cellular or syncytial trophoblast or both.

Gey, Jones and Hellman ('38) and Jones, Gey and Gey ('43) have demonstrated that tissue cultures containing actively growing trophoblast produce appreciable quantities of chorionic gonadotrophic hormone even after repeated transplantation over a period of several months. Furthermore, their observations, as well as previous ones by Friedheim ('29) and Sengupta ('35), indicate that it is the cytotrophoblast rather than the syncytium that survives and proliferates in tissue cultures. Syncytium, in so far as it arises, is small in amount and atypical in appearance and is derived from the cellular form. These observations indicate that the cytotrophoblast is the source of the hormone.

Tenney and Parker ('39) remark that the amount of this hormone excreted in women suffering from hydatidiform mole or chorionepithelioma corresponds roughly to the amount of trophoblastic "cells" and that a mole with cystic villi and slight trophoblastic proliferation gives a low titer. These findings suggest that actively proliferating cytotrophoblast is more important in the production

of chorionic gonadotrophic hormone than the syncytium derived from it. Further, Wislocki and Bennett ('43) have emphasized that the curve of excretion of gonadotrophic hormone in the pregnant woman parallels approximately the rise and decline of the cytotrophoblast rather than simulating the slow, steady increase in the amount of syncytial trophoblast.

The Production of Placental Steroid Hormones. Histochemical procedures for locating steroid lipids, to which the steroid hormones belong, have been developed in recent years. Steroid hormones are produced by the gonads, the placenta and the adrenal cortex. No single method is available for identifying such compounds in tissue sections but by the use of a combination of reactions, the sum of which characterizes ketosteroids (but no other known type of compound), they can be identified with some assurance (Bennett, '40; Dempsey and Wislocki, '46).

Frozen sections of formalin-fixed material are prepared. (1) Since all ketosteroids are soluble in acetone at room temperature, all of the subsequent methods will be negative following extraction of the sections in this solvent. (2) The steroids, along with other lipids, are sudanophilic and hence will be stained with sudan dyes. (3) Because of their ketone groups, the steroid hormones (but not cholesterol) will react with phenylhydrazine to produce yellow hydrazones and will recolorize leucofuchsin (Schiff's reagent) to produce a purple color. (4) The unsaturated steroids exhibit autofluorescence when illuminated by ultraviolet light. The characteristic fluorescence of this class of compounds is greenish or yellowish. Consequently, if an unstained section is viewed with ultraviolet light, the steroid droplets will appear yellow or green on a bluish background. (5) Because of the ionization of their terminal radicals, steroids orient themselves as birefringent spherocrystals within the lipid droplets of the cells that secrete or store them. Consequently, if an unstained section is examined in polarized light, birefringence will be seen.

Birefringent, sudanophilic lipid droplets are abundantly present in the trophoblastic syncytium throughout gestation. They are acetone soluble, react with phenylhydrazine (Wislocki and Bennett, '43), give a positive *Schiff* reaction, and exhibit yellowish green autofluorescence (Dempsey and Wislocki, '44). The cytotrophoblast including the Langhans cells is devoid of lipid droplets, while the sudanophilic droplets in the decidual cells and in the epithelium of the uterine glands are neither birefringent nor fluorescent. From these observations the conclusion is drawn that the syncytium is very probably the site of origin of the placental steroid hormones.

The Occurrence of Cytoplasmic Nucleoprotein in the Trophoblast. The cells of the body contain two types of nucleoprotein which differ from one another in the possession of pentose sugars which may be either ribose or desoxyribose. Nucleoproteins being acid in character have an affinity for basic dyes and hence are said to be basophilic. Desoxyribonucleoprotein is present exclusively in the chromatin of nuclei, whereas ribonucleoprotein occurs in the nucleoli as well as frequently in the cytoplasm of cells. The former can be identified histochemically by the Feulgen reaction and the latter by its solubility in ribonuclease. These two reactions serve also to distinguish nucleoproteins from other basophilic

constituents of cells, for example, acid mucopolysaccharides. These substances can also be distinguished from one another by means of a photometric method based upon the relative affinities of basophilic constituents of cells for methylene blue (Dempsey and Singer, '46; Dempsey, Bunting, Singer and Wislocki, '47).

The human placenta has been studied by these various means (Dempsey and Wislocki, '45) and it has been shown that both the cytotrophoblast and the syncytium are very rich in cytoplasmic basophilia attributable to the presence of ribonucleoprotein. The cells of the cytotrophoblastic columns and cell islands contain conspicuous dark clumps of basophilic material in their cytoplasm and these are readily digested by ribonuclease. The cytoplasm of the syncytium is characterized by a zone of deeply stained basophilic material surrounding the nuclei and this is also removed by exposure to ribonuclease. The basophilic zone characterizing the syncytium stains deeply in the early months of gestation but its staining diminishes slowly as the placenta ages. It is noteworthy that as the basophilia of the syncytium diminishes with advancing gestation both acid and alkaline phosphatases increase greatly. In contrast to the other elements of the trophoblast, the Langhans cells of the chorionic villi possess relatively little cytoplasmic basophilia.

Nucleoproteins are generally concentrated in cells in which the synthesis of protein is actively taking place where they are thought to act as enzymes in the formation of other proteins (cf. Dempsey and Wislocki, '46). In the placenta, cytoplasmic ribonucleoprotein is especially plentiful in the cytotrophoblast of the trophoblastic shell and cell columns and in the trophoblastic syncytium. We interpret its presence in these regions as being indicative of active protein synthesis. In the case of the cytotrophoblastic shell and cell columns it might conceivably be related to the synthesis there of the chorionic gonadotrophic hormone. In the syncytium, on the other hand, where it is present particularly in the first months of gestation, it might well represent the primary site of synthesis of the proteins of the fetal blood plasma, a function presumably taken over later by the hepatic cells when the fetal liver becomes sufficiently differentiated.

The Occurrence of Glycogen in the Trophoblast. Glycogen occurs widely in the placenta. It is especially abundant in the cytotrophoblast of the cell columns and islands and the trophoblastic shell. Little occurs normally in either the Langhans cells or syncytium clothing the chorionic villi. Some is present in the stroma of the chorionic villi. It occurs in large quantities in the glandular epithelium and in the decidual cells of the endometrium. Dempsey and Wislocki ('44) have expressed the opinion that it occurs especially in regions of the placenta that are relatively avascular and therefore poorly supplied with oxygen, and that under anaerobic conditions it may provide a readily available source of energy. In the cytotrophoblast of hydatidiform moles, unusually large amounts of glycogen are encountered (Wislocki and Dempsey, '46b) in keeping with the relative avascularity apparent in these pathological formations. Similarly, in 2 placentas of the 3rd month removed therapeutically because of maternal cardiac disorders, we gained the impression that the syncytium and Langhans cells covering the villi contained increased amounts of this substance.

The Occurrence of Mitochondria and Golgi Apparatus in the Trophoblast. Mito-

chondria are extremely abundant in the syncytial trophoblast in the early part of gestation and diminish in number as the placenta ages (Wislocki and Bennett, '43). In the Langhans cells and cytotrophoblast in general there are fewer of them. Recent investigations indicate that these bodies are composed in part of phospholipids.

The Golgi apparatus is demonstrable in both cytotrophoblast and syncytium; in the latter it occurs in the form of threads extending rather diffusely through the cytoplasm in the nuclear zone (Wislocki and Bennett, '43). These cell structures have also been shown to contain phospholipids as one of their components.

The Occurrence of the Indophenol Oxidase and Reduction-Oxidation Reactions in the Trophoblast. The indophenol oxidase reaction was carried out with the nadi reagents on fresh, teased villi and unfixed sections of a placenta of the 6th week of pregnancy (Dempsey and Wislocki, '44). By this procedure indophenol blue was produced in the trophoblastic syncytium, a reaction which is believed to reveal the presence of the cytochrome oxidase-cytochrome C system. This system, because of its almost universal occurrence, and because of the marked decline in metabolism after cytochrome inhibition, is thought to provide one of the principal energy transfers in animal tissues. The observation, therefore, of the amount of indophenol blue produced permits a rough estimate of the amount of oxidative activity in a given region. The stroma of the villi in contrast to the syncytium did not stain with indophenol.

Similarly, a series of reduction-oxidation indicators was applied to fresh, teased villi and fresh, frozen sections. The syncytial trophoblast concentrated all of the dyes in their oxidized form, whereas the stroma of the villi reacted far less intensely. These results indicate that the syncytial layer is maintained in air at a more positive redox potential than are the deeper parts of the villi and are in keeping with the similar distribution of indophenol oxidase.

Summary of the Cytological and Histochemical Characteristics of the Trophoblast. The *cytotrophoblast* of the trophoblastic shell, cell columns and cell islands, the *Langhans cells* of the chorionic villi, and the trophoblastic *syncytium* have different cytological and histochemical characteristics as well as distinctive functions.

The *cellular trophoblast* constitutes the germinal tissue from which the syncytium is secondarily derived.

The *cells of the trophoblastic shell, cell columns and cell islands* are characterized by strong cytoplasmic basophilia (ribonucleoprotein) and the presence of glycogen. On the other hand, fats and ketosteroid lipids are lacking, but mitochondria (phospholipids) are present. Acid and alkaline phosphatases occur to a minor extent. In the first months of pregnancy, these cells liberate proteolytic agents capable of attacking and destroying the cellular and interstitial elements of the endometrium. These enzymes can induce hyperemia, hemorrhage and edema, besides digesting epithelium, capillary walls, decidual cells, reticulum and collagen fibers, and mucoproteins. The cytotrophoblast probably also forms and liberates the chorionic gonadotrophic hormone.

The *Langhans cells* (cytotrophoblast of the chorionic villi) exhibit abundant mitoses and by cytomorphosis give rise to the trophoblastic syncytium clothing

the chorionic villi. Unlike the cells of the peripheral trophoblast (shell, columns, etc.) they exhibit relatively little cytoplasmic basophilia and contain little or no glycogen. They contain no fats or ketosteroids, relatively few mitochondria (phospholipids) and only slight amounts of acid and alkaline phosphatases. They may possibly also produce chorionic gonadotrophic hormone. There is no evidence indicating that they liberate proteolytic enzymes.

The trophoblastic *syncytium* possesses small hyperchromatic nuclei which appear to undergo amitotic division. The cytoplasm of the syncytium contains more demonstrable constituents than either the Langhans cells or the peripheral cytotrophoblast. It contains a large amount of basophilic substance (ribonucleoprotein) which diminishes as gestation advances. A great many lipid droplets are present which are birefringent, react positively with phenylhydrazine and Schiff's reagent, exhibit yellowish green autofluorescence and are soluble in acetone. Mitochondria are extremely abundant and a diffuse Golgi net is demonstrable. It contains acid and alkaline phosphatases both of which increase in amount as the placenta ages. Indophenol oxidase (nadi reaction) and reduction-oxidation reactions (redox potential) are also demonstrable.

The presence of lipid droplets giving the group of reactions listed above indicates that the syncytium is the site of formation of the placental steroid hormones. It seems likely also that the store of ribonucleoprotein (cytoplasmic basophilia), present in the syncytium during the first months of gestation, represents an important site of synthesis of proteins required by the growing embryo.

CONCLUSION

The recent investigations of placental histochemistry reviewed here indicate that the functions of this organ are more numerous and more complex than hitherto believed. Until recently, the opinion prevailed quite generally that placental function could be explained best on the assumption of a resemblance to a semipermeable membrane operating on the principle of Donnan's equilibrium.

The observations presented here indicate that the trophoblast has a complex organization involving proteins, carbohydrates and lipids and including a variety of enzymes. It seems likely that protein synthesis takes place in the trophoblast in connection with large amounts of ribonucleoprotein demonstrable there. Evidence is also adduced indicating that the trophoblast secretes proteolytic and cytolytic enzymes. Finally, histochemical evidence is presented which indicates that the trophoblast is the site of origin of chorionic gonadotrophin (in the cytotrophoblast) as well as placental steroid hormones (in the syncytium). Consequently, in addition to its functions as an organ subserving the catabolic and anabolic growth requirements of the fetus, the placenta is an endocrine organ which appears to synthesize and secrete several different hormones.

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DISCUSSION

CHAIRMAN HERTIG: I think you have had ample illustration why Dr. Wislocki is and will continue to be regarded as one of the world's eminent placentologists. Those of us who had

a chance to work with him or to be stimulated by him have known this for some time. I would like, therefore, to take this opportunity to express publicly my debt of gratitude to him for his part in stimulating me to investigate some of the anatomical features of the early human ovum.

There was one thing which Dr. Wislocki mentioned, namely, the proteolytic activity of the trophoblast and its effect on the endometrium which needs amplification. He cited the 11-day specimen that Dr. Rock and I found some years ago as exhibiting this activity on the endometrium opposite the implantation site, a contra-coup phenomenon, as it were. That was very definite in that particular specimen but it is not universally so in the other early ova that we found. Whether its presence in the 11-day stage was merely one of the normal anatomical variants of this proteolytic power of trophoblast or not, I don't know.

His mentioning of the sites of iron and where they are found in the placenta brings to mind—and he touched on it in passing—the sites of calcification which are present in the maturing and pathologically aged placenta. Those sites of grossly demonstrable calcification are seen in the ground substance of what has also been called fibrinoid material as well as in the basement membrane just beneath the degenerating syncytium.

I was very much interested in the comments he made on the mucopolysaccharides that occur between the decidual cells and the possible role of these substances as a protective material against the undue invasion of trophoblast. It called to mind a very dramatic incident which occurred at the Lying-in Hospital, associated with the spontaneous perforation of the uterus by a hydatidiform mole, itself a potentially malignant tumor. It was interesting to note, whether it was a pure coincidence or not, that the reaction similar to what Dr. Wislocki has shown, namely, the fibrinoid material between the decidual cells and occasionally between muscle cells was absent in this particular case. It is possible that here was an invasive mole, ordinarily kept within the boundaries of the myometrium, which had been able to invade and even perforate the uterus without any apparent barrier to its invasion.

Now I would like to throw this very stimulating paper open to general discussion.

DR. W. B. A. ATKINSON: Dr. Wislocki's remarks on the site of chorionic gonadotrophin formation bring to mind the pituitary gland where basophilia has long been associated with the formation of the gonadotrophic hormones. If the ribonucleoproteins are concerned with the synthesis of these hormones which are mucoproteins, one would expect to find mucoproteins in the basophilic cells. This has been reported to be the case in the pituitary. It is odd to note, however, that in the case of the placenta the present authors do not find mucoprotein in the basophilic cells which they believe to be sites of chorionic gonadotrophin formation.

CHAIRMAN HERTIG: I think it would be clearer if you answered individually.

DR. WISLOCKI: In regard to the histochemical demonstration of mucoproteins, only a limited number of them, namely, the more acid members of the mucopolysaccharide series, can be stained with metachromatic dyes. Neither the cells of the pituitary nor the cytotrophoblast exhibit metachromasia and consequently they do not appear to contain acid mucopolysaccharides. The pituitary and chorionic gonadotrophins are known to contain mucopolysaccharides but these are probably neutral or so feebly acid that they are not specifically brought out by metachromatic dyes.

Catchpole and Gersh have described a positive periodic acid-Schiff reaction in certain pituitary cells. Their results led us to believe that using the periodic acid technique we might demonstrate the mucopolysaccharide of the chorionic gonadotrophic hormone in the cellular trophoblast. This we attempted after first removing the glycogen which constitutes a conflicting element in the cytotrophoblast by preliminary treatment of the sections with saliva. We were, however, unable to demonstrate any specific reaction with the periodic acid-Schiff method after the glycogen had been removed. Why this method brings out the carbohydrate groups in mucus and some related substances but fails with other mucopolysaccharides we are unable to explain. We have not been successful in demonstrating the presence of chorionic gonadotrophin in the placenta by this method.

DR. A. E. RAKOFF: I should like to ask Dr. Wislocki whether he has applied his methods of studies to the membranes and particularly whether there is any evidence of similar lipids possibly suggesting steroid hormones in either the amnion or chorion, and also whether he has any evidence of any substances in the placenta which would inactivate steroid hormones.

DR. WISLOCKI: We have no information on whether steroid hormones are present in the amnion and membranous chorion, nor have we given any thought to your second question about possible substances that would inactivate steroid hormones.

PLACENTAL DYSFUNCTION IN ECLAMPTOGENIC TOXEMIAS

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The complex and multiple functions of the trophoblast have been ably discussed by Doctor Wislocki in the preceding paper. It would not be farfetched for any student of eclamptogenic toxemia to suggest that this disease is associated with disturbances in the secretory activity, functions of transmission and endogenous metabolism of the placenta. To discuss these dysfunctions with any degree of assurance is another matter, for you will agree that we are only beginning to understand the physiology or biochemistry of the placenta in normal pregnancy. Any attempt to correlate placental dysfunction, about which we know little, with another intangible, the pathogenesis of preeclampsia, is presumptuous indeed, for in doing so one cannot avoid the use of conjecture. For this, however, I offer no apology; because working hypotheses must always play an important though subsidiary role in research, even if they do no more than provoke thought.

.The purpose of this discussion is three-fold: First, to develop the thesis previously suggested (1), that a diffuse hypoxia or relative maternal ischemia of the placenta is the proximate or precipitating cause of preeclampsia and of the associated placental dysfunctions; and to show how the various mechanisms for initiating such uterine ischemia are related to the known predisposing causes of preeclampsia. Second, to give both objective and circumstantial evidence that such a diffuse disturbance of the maternal blood supply to the trophoblast may lead to degeneration or cytolysis of the syncytium, and to show how the resultant liberation of active proteins into the maternal blood might well produce systemic effects. Third, to discuss the known placental dysfunctions which are associated with eclamptogenic toxemias and to relate them to this alleged premature degeneration of the trophoblast. The lack of time permits reference to only a few of the countless contributors to these various concepts.

We must, at the outset, accept the prevalent belief, for which there is good evidence (2), that the nourishment of the trophoblast is from the maternal blood with which it is in contact. One of the chief reasons for this belief is the fact that the placenta will maintain normal secretory function and does not degenerate after primary death of the fetus. Experimentally it will continue to function till term even after removal of the fetus (3). A reasonable corollary to this belief is the concept that the metabolic needs of the trophoblast are determined by its own endogenous metabolism, plus any energy requirements necessary for the transfer of materials to and from a living fetus. The primary death of a fetus, according to this view, only serves to reduce the energy demands of the placenta. The supply of such energy (in the form of oxygen, utilizable substrates and essential materials) is proportional to the total volume of maternal blood flowing through the placental "lake" per unit of time. Relative ischemia of the placenta

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Dr. WISLOCKI: We have no information on whether steroid hormones are present in the amnion and membranous chorion, nor have we given any thought to your second question about possible substances that would inactivate steroid hormones.

not such systemic diseases as diabetes, nephritis, and essential arteriolar hypertension directly affect the arteries of the uterus and cause circulatory impairment? The oxygen supply to the trophoblast may be reduced by such maternal diseases as severe sickle cell or hook-worm anemias, in both of which the incidence of preeclampsia is reported to exceed 50 per cent. In addition to those factors producing ischemia, as outlined in the table, it is conceivable that the trophoblast might be indirectly and again diffusely injured by severe maternal deficiencies such as beri-beri or a marked protein deficiency, which are also predisposing causes.

In other words, we have in such a working hypothesis a means of establishing a single common denominator for all of the strange and varied states and disorders known to be associated so often with the development of eclamptogenic toxemia. I am not aware that any other hypothesis can effect such a correlation. It should be pointed out, furthermore, that many of our therapeutic measures for preeclampsia, such as complete bed rest, quietude, vasodilating drugs, sedatives, caudal anesthesia and the rupture of membranes would also be expected on physiologic grounds to improve the maternal perfusion rate of the placenta.

What evidence, either direct or circumstantial, exists for this alleged ischemia or hypoxia of the placenta? Obviously the impairment must be prolonged for hours or days to produce degenerative changes. It would not be anticipated, for example, that the intermittent ischemia and reactive hyperemia of normal labor would injure the placenta any more than it would the fetus. It is unfortunate that no one has yet devised means of measuring the uterine blood flow in pregnancy comparable to the methods used for estimating rates of flow through the heart, kidneys and liver. We know that the fetus often dies during preeclampsia and that while living its rate of growth is slowed. Other than this, we must turn to the delivered placenta itself for evidences of past injury, and here I can only depend upon the published reports of others.

One of the more extensive studies is that of Tenney (7) and Tenney and Parker (8) who described a marked increase in the degree of degeneration of the syncytium clothing the terminal villi in cases of preeclampsia. They believed that such diffuse degeneration began before the onset of symptoms, and that in every case where widespread damage was manifest, large amounts of protein were found in the urine. Hypertension, nephritis, or chronic pyelonephritis only produced such damage when there was superimposed preeclampsia. Wislocki and Dempsey (9) in a comprehensive examination of the placentas from two toxemias occurring early in pregnancy concluded that there was histochemical and cytological evidence of advanced aging of the syncytium. They further state that their histochemical examinations of the toxemic placentas indicate that there is probably some impairment of the blood supply as well as a certain degree of anoxemia of the chorionic villi in this disease. There is not a universal agreement among pathologists about the occurrence of such diffuse microscopic changes in toxemic placentas, but I find no published reports which either deny or confirm Tenney's findings. In either case, we need not insist that functional changes in an organ must always be reflected by morphologic changes.

There is an approach other than the strictly morphologic one, and that is the

may then be defined in the usual manner as a marked reduction in the ratio of maternal supply to metabolic demand.

Let us now examine some of the various and rather self-evident mechanisms by which the nutritional support of the trophoblast may be reduced (Table 1). An interference with the effective perfusion of the intervillous channels may be achieved by transmitted compression of the placenta brought about by an increased hydrostatic pressure within the uterus (4). This may be from an increased pressure from within, as in multiple pregnancy and hydramnios, or from increases of intra-abdominal tension from more unyielding abdominal walls, as in primiparae or obesity. I have purposely listed those examples in which the

TABLE I

FACTORS WHICH MAY PRODUCE OR ACCENTUATE RELATIVE ISCHEMIA OR HYPOXIA OF THE PLACENTA	EXAMPLES (ALSO KNOWN PREDISPOSING CAUSES OF PREECLAMPSIA.)
I. Increased hydrostatic pressure within the intervillous "Lake".	
A. From increased hydrostatic tension within the uterus	Hydramnios Twins Triplets
B. From increased intraabdominal pressure	Primiparity Obesity with short stature
II. Diffuse mechanical compression of uterine blood vessels	Labor
III. Vasomotor constriction of spiral arterioles, through autonomic nervous system	Extreme emotional tension or shock
IV. Systemic disease producing a widespread effect upon the arteries of the uterus	Pre-existing hypertension, nephritis, (?) diabetes mellitus
V. Direct hypoxia of the trophoblast by severe maternal anemia	Anemia of hook-worm disease, sickle cell anemia

actual incidence or the frequency of onset of preeclampsia is markedly increased, so that we have, in effect, a cross-correlation.

In a recent study, Parvcainen (5) found the incidence of toxemia to be twice as high in women bearing twins and three times as high with triplets. From this fact alone, he concluded that relative ischemia of the gravid uterus must be the cause of toxemia.

Contractions of the myometrium may compress the small arteries as they traverse at right angles through the muscle bundles. We also know that the arterioles are supplied with autonomic nerves, and at least in the non-pregnant state may be influenced through the central nervous system. As an analogy, Doctor Chesley and his coworkers (6) have shown us that simply placing the hand in ice water may reduce the volume flow through such an organ as the kidney and even cause transient proteinuria. I wish there were time to discuss the psychosomatic aspects of preeclampsia, but it should please those psychiatrists who believe in the psychosomatic precipitation of eclampsia to know that a *modus operandi* for this view has not been omitted from consideration. Could

glycolysis rate of toxemic placentas, and perhaps this is a more sensitive measure of reduced syncytial function than the aerobic rate.

In at least the severe or prolonged cases of preeclampsia, then, we have cytologic, histochemical and metabolic evidence for some disruption in the functional integrity of the trophoblast. This must be regarded as different from the normal, more orderly and probably purposeful thinning-out process referred to as aging of the placenta.

Let us consider next the sequence of events which syncytial degeneration may now initiate. During pregnancy, of course, there is the unique situation in which the maternal blood comes into contact not only with vascular endothelium, but with fetal epithelium as well. Cytolysis or an abnormal liberation of protein from this epithelium would be the logical result of injury from hypoxia or ischemia. Depending on the rate of blood flow and the rapidity of syncytial damage, it would be inevitable that some of the cytoplasmic contents of the syncytium would be liberated into the maternal blood.

We know from the studies of Chargaff (12) that the placenta is one of the richest sources of thromboplastin in the body, and the syncytial cytoplasm must contain large amounts. The most likely primary result of liberating this macromolecule into the intervillous sinus would be the deposition of fibrin from a moving current of blood (as in the procedure of defibrination) or a complete intervillous thrombosis in a relatively stagnant pool. Both processes lead to so-called "infarcts" and often occur in the normal placenta. It would be anticipated, however, and it is generally agreed that the occurrence of such "infarcts" is somewhat more common in eclamptogenic toxemias (13, 14).

A secondary result of liberating thromboplastin into the maternal blood would be its entry into the systemic circulation. We are indebted to Charles Schneider (15) for identifying the lethal factor of human placental extracts as thromboplastin, when such extracts are injected into the tail veins of mice. In these animals, the liver appears to be the primary site of fibrin deposition and capillary thrombosis. The same is true of human eclampsia, as has been indicated by liver biopsy studies during life (16) as well as by autopsy studies. The production of similar lesions was demonstrated by Doctor Dieckmann in dogs (17), and while he called his material "tissue fibrinogen", it is more likely in retrospect that he was dealing with tissue thromboplastin. Indeed, the thrombokinase portion of this hypothesis was proposed by Dienst many years ago.

But thrombokinase is only one of countless biologically active proteins contained within living cytoplasm, and I wish to hazard the guess that in eclampsia the elusive "toxins", about which we know nothing, will nevertheless be found among the active proteins normally locked within the cell boundaries of the trophoblast. There are three reasons for this suspicion. First, is the well-known fact that the maternal visceral lesions observed in fatal eclampsia are not normally seen in the fetus. This suggests that the offending materials which produce such widespread damage cannot themselves traverse the placenta. Second, such substances are likely to be "active", not only because most intracellular proteins are probably enzymes (18), but because natural inhibitors for such pro-

study of the metabolism of normal and toxemic placentas *in vitro*. I wish to refer briefly to an incomplete study (10) in which we have measured the rate of oxygen consumption of several preeclamptic placentas. (Figure 1). The Q_{O_2}, expressed as microliters of oxygen consumed per milligram dry weight of placental tissue, is somewhat like the basal metabolic rate of an individual. Like the decline of a human B.M.R. from age 2 to 70, the Q_{O_2} declines from about 7 at the second month to a mean of 2 at term, an indication, perhaps, of the normal aging process. Each point represents the mean of 6 observations from various healthy portions of each placenta. This is simply a confirmation of Wang and Hellman's data (11). Here we see that in the last trimester the rate of decline, calculated by the method of least squares, is statistically significant. Differences in the respiration of tox-
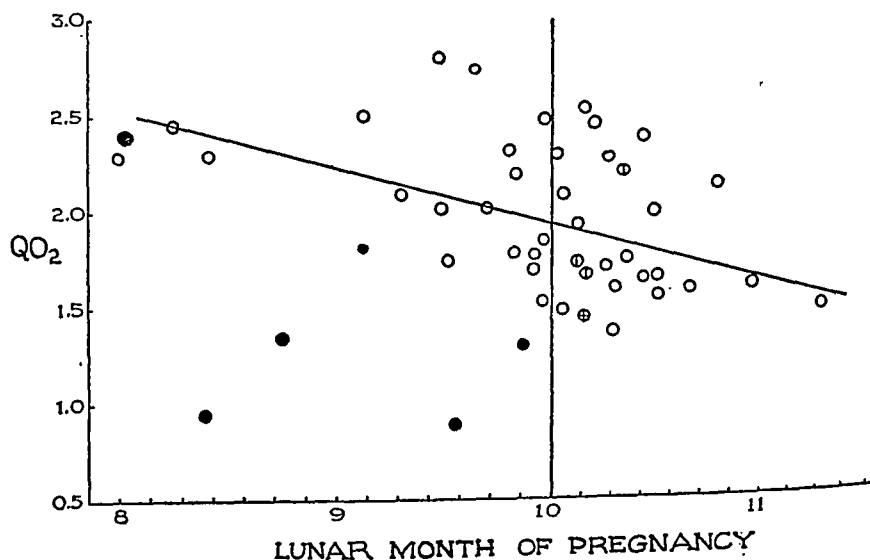
FIG. 1. Circles: normal gravidae; solid circles: preeclamptic patients.

emic placentas are not too convincing, for there are several moderate grades of preeclampsia illustrated here in which the rates are well within normal limits. But there are 4 very aberrant, low rates occurring in severe preeclampsia and eclampsia. In these cases, the toxemia was found to have existed for several weeks, whereas the others were acute and of short duration. Histologic examination of the placenta in 7 cases, using Tenney's criteria, shows more marked syncytial degeneration of the terminal villi in those with the reduced oxygen consumption. This suggests that the reduced rate is due to a fewer number of functioning cellular units per milligram of tissue. It could, on the other hand, be due to a specific enzymatic "bottleneck" in the oxidative chain. We have measured the succinic dehydrogenase and cytochrome oxidase activities in homogenates from these same severe toxemia placentas, but there is less reduction in either of these systems than in the endogenous Q_{O_2}. Doctor Hellman informs me that there is a more consistent reduction in the anaerobic

course of the disease. We have treated 4 preeclamptic women by full heparinization for a 3 day period. In 1, in which hypertension and proteinuria were the only symptoms, the clinical course was uninfluenced. In 2, there was a decrease in proteinuria and a moderate reduction of blood pressure. In the 4th and only case with hepatic symptoms, there was a dramatic disappearance of epigastric pain and liver tenderness. Within a few hours after discontinuance of the heparin infusion, the epigastric pain, proteinuria and hypertension recurred severely, and termination of the pregnancy became necessary. Such preliminary results suggest that circulating thromboplastic proteins might be important in producing the hepatic lesions, but may or may not be concerned with the hypertension, edema, or the laminated thickening of glomerular capillary walls (26).

To discuss the possible nature and origin of other toxic substances would lead us into much more ethereal speculation and cannot be undertaken here. Perhaps Doctors George and Olive Smith have identified an important protein in their necrosin-like "menstrual toxin" (27). It is unlikely, however, that the fibrinolytic enzyme of normal or menstrual serum ("plasmin") is a toxin, for Seegers, Loomis and Guest (28) have been able to purify this material and find that it is not toxic on intravenous administration to animals. The placenta does not contain renin (29), but we have noted that it does contain an elusive protein which consistently causes a delayed pressor response following intravenous injection into rabbits (30). In the presence of experimental renal hypertension, we have found that the placenta causes a reduction rather than an increase of the hypertension (31).

At the present time, we doubt that the delayed rises in blood pressure following acute uterine ischemia in pregnant dogs (32), are dependent upon the placenta, for similar rises may be observed when only deciduomata are present (33). Our efforts in the past to produce a chronic uterine ischemia without death of the fetus in pregnant rabbits were unsuccessful. It has been postulated that one of the most potent of pressor amines, hydroxytyramine, might arise under conditions of hypoxia, but we have found no trace of dopa decarboxylase in either normal or eclamptic placentas (34). This is, incidentally, one of the few enzymes looked for in the human placenta and not found.

The origin of the hypertension, then, remains unexplained, but we would like to feel that it is not entirely purposeless, that perhaps it is a compensatory attempt to increase the effective perfusion pressure of either the kidney or the placenta.

Regardless of the nature of substances which might be released from the syncytium to produce systemic effects, we should obviously shift our attention away from the "infarcts", which, perhaps in the wisdom of nature, have excluded portions of the placenta from contact with circulating maternal blood. Such a process of injury followed by exclusion of damaged tissue often occurs normally, and in preeclampsia might ultimately lead to an equilibrium, even at the expense of fetal life. Such events may be exemplified by intercurrent eclampsia, in which the survival of an infant is a rare occurrence indeed.

The surface of syncytial clothed villi exposed to the maternal blood at term

teins are usually present in normal blood. This would explain our failure to produce any part of the eclamptic syndrome by the transfer of blood from eclamptic women to non-toxic pregnant recipients (19). Third, may I call your attention to the rate of decline of post-partum eclampsia with each twelve hour period. (Figure 2.) Data from the New York (20), Chicago Lying-in (21), and Los Angeles County (22) Hospitals have been combined and plotted as per cent of total eclamptics on a three-cycle logarithmic scale. The "die-away" curve becomes a straight line, and if this is projected to infinite smallness, then the occurrence of true eclampsia more than 6 or 8 days postpartum would have to be viewed with suspicion. The occurrence of postpartum eclampsia has some-
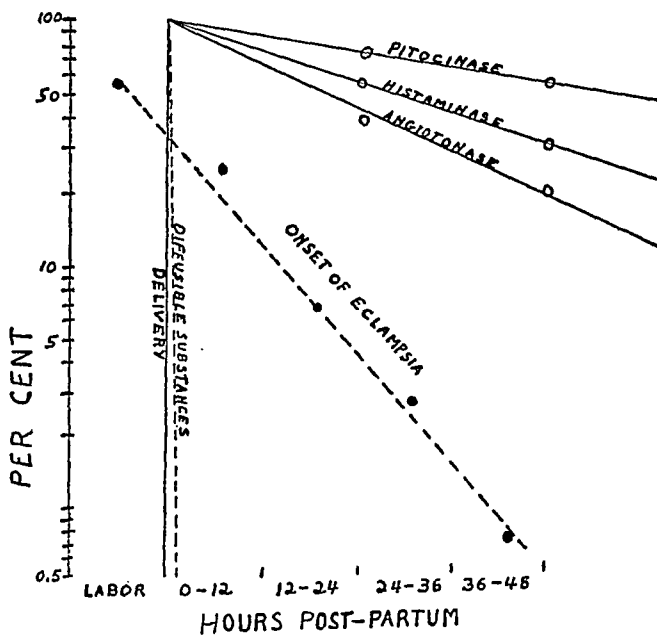
Fig. 2

times been used as an argument against its placental origin, but observe the rate of disappearance from the maternal plasma for three active proteins which we believe originate as a product of the trophoblast. One is for Pitocinase (23), an enzyme which inactivates the posterior pituitary hormone, one is for histaminase (24), and the third for angiotonase (or hypertensinase) (25). (The slope for thromboplastin disappearance is probably less steep and that for the chorionic hormone more steep because of differences in molecular size, but quantitative data are not available.)

The important thing to note is that readily diffusable and quickly destroyed substances such as tyramine, histamine, guanidine, post-pituitary hormone, etc., all disappear from the blood stream at an extremely rapid rate, and it would be difficult to explain the initiation of toxemia postpartum by any such substances.

Now if thromboplastin plays any role in producing eclamptogenic toxemias, then heparinization of the patient, as suggested by Schneider, should alter the

the past decade regarding the present status of the role which the placenta may play in the production of eclamptogenic toxemia. As a tentative hypothesis, it is suggested that a relative ischemia, or hypoxia of the placenta may produce a diffuse injury to the trophoblast. The various means by which this, in turn, may be initiated correlate fairly well with the known predisposing causes of eclamptogenic toxemia. That portion of the trophoblast which is not sealed off by those processes giving rise to "infarcts" may contribute toxic materials which produce systemic lesions. Such materials are most likely to be of large molecular size, and one of them may be thromboplastin. During toxemia, there are definite objective evidences for dysfunction of the placenta, in regard to the elaboration of both enzymes and hormones, and in its capacities for transmission. Such dysfunction appears to be associated with and probably caused by this diffuse trophoblast injury.

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has been estimated to be 70 square feet, and the combined length of the villi to be about 20 miles (35). It would be expected that any diffuse injury to such a tremendous epithelial surface by ischemia or hypoxia might alter its secretory functions as well as its capacities for transmission. We believe that the logarithmic increase in either Pitocinase or histaminase concentration in the plasma during pregnancy is probably due to the secretion of these enzymes by the syncytium, because the rate of increase perfectly parallels the rate of placental growth till term. Notice that in the presence of toxemia, the Pitocinase values are disturbed (Ref. 23, Figure 3). Quantitative studies of histaminase by Ahlmark (Ref. 24, Figure 19) show a similar type of disturbance. Abnormal values likewise occur in the plasma concentrations of angiotonase (25) and glucuronidase (36). Why the toxemias produce abnormal concentrations in both directions is not yet known. We feel, however, that these phenomena are the result, not the cause of placental dysfunction.

In a similar manner, the well-known premature and rather consistent decrease in the urinary excretion of total steroids (37, 38) in eclamptogenic toxemias may be interpreted as being secondary to the syncytial injury. The circumstantial evidence for the production of these steroids by the syncytial cells, as presented by Doctor Wislocki, is rather strong. On the other hand, the serum concentration and urinary output of the chorionic gonadotrophin is maintained or even elevated in the presence of toxemias. The reason for this has been the subject of much discussion, and it may well be that the Smiths' hypothesis is correct (39), namely that there is a failure of syncytial utilization of this protein. May I suggest, however, that a unified concept for the origin of chorionic hormone fluctuations in both early and late pregnancy, normal or toxemic, might be equally tenable. This simply assumes that differences in the output of protein and steroid hormones primarily reflect differences in the rates of production. The evidence is very strong that the chorionic gonadotrophin is produced chiefly by the Langhans cells, while the steroids are probably produced by the syncytium. The ratio of hormone production, therefore, would reflect the ratio of one type of cell to the other. Wislocki and Bennett (40) have suggested that the Langhans cells actually persist till term and that they constitute a germinal bed, giving rise to the syncytium. The latter apparently has no power of mitotic reproduction. If the trophoblast receives a sublethal injury in the manner we have suggested, is it certain that it is the only epithelial structure in the body that cannot respond to such injury by growth or repair? We recall that when full-term placental tissue has been explanted and cultured, it is presumably the Langhans cells which multiply and which continue to produce chorionic gonadotrophin (41). If Wislocki and Bennett's theory is correct, then the only means the trophoblast has of proliferating in response to sublethal injury is by the growth of the Langhans cells. That quantitative disturbances in the ratio of Langhans cells to syncytium have not been detected by histologic methods in the injured full term placenta is not surprising when we read that even one Langhans cell can only be found "by diligent search" (40).

To summarize, this has been in effect a consideration of the contributions of

of protein catabolism. The typical effect of this toxin upon test animals is vascular damage with vasoconstriction, increased capillary permeability and edema. The obvious conclusion from our studies is that any condition which introduces any one of these three, viz.; inadequate blood supply, hormonal deficiency or tissue catabolism, will constitute a predisposing factor towards the eventual development of all three. When all three are present and augmenting one another, the uterus either empties itself, or the fetus dies, or pre-eclampsia or eclampsia becomes clinically manifest.

It is becoming increasingly apparent from the work of many people throughout the country that the whole enzyme system is upset in any condition involving vasoconstriction and ischemia. Dr. Page has added important contributions to this field. The fibrinolytic enzyme that we have found in menstrual discharge, in exudative material from tissue injury and in the circulating blood of menstruating and pre-eclamptic women is simply another indication of the effect of ischemia and tissue damage upon the enzyme system. Although this fibrinolytic enzyme and catatoxin have gone hand in hand in all the studies that we have done, we have never been ready to say that the two were identical. Perhaps further elucidation of the enzymes involved in ischemia will shed some light on the mechanism of toxin formation or release.

Dr. Page suggested that the increased level of chorionic gonadotrophin in toxemic patients might actually reflect increased production due to the fact that the cells of the cytotrophoblast are able to proliferate and the syncytial cells, that presumably secrete the steroid hormones, are not. He has hypothesized that such proliferation might be a response to tissue damage. This is an interesting thought, but not, so far as we know, substantiated by the evidence at hand. At the termination of normal pregnancy, there is an increase in the level of chorionic gonadotrophin in the blood. Histological and histochemical studies of the placenta have revealed no increase in cytotrophoblast to account for this. Furthermore the very marked rise in the level of chorionic gonadotrophin in the blood of pre-eclamptic patients is not associated with any increase in cytotrophoblast. In fact, I believe that Dr. Wislocki and Dr. Dempsey noted an unusual degeneration of the cytotrophoblast in the two toxemic placentas that they have studied by histochemical techniques.

We suggested many years ago, as a working hypothesis, that the rise in serum chorionic gonadotrophin at term and in pre-eclampsia reflects a failing utilization of this hormone for the production of estrogen and progesterone. The same suggestion has been made by Dr. Venning and Dr. Browne, and the more recent histological and histochemical findings of Drs. Wislocki and Dempsey in toxemic and term placentas are in keeping with this, if one accepts their evidence that the syncytial trophoblast secretes the steroid hormones.

DR. GEORGE VAN S. SMITH: The only thing I might add to Mrs. Smith's discussion is that I should like to have Dr. Page include the decidua with the syncytium as part of the tissues which are disabled due to the process which goes on in toxemia.

CHAIRMAN HERTIG: I would like to add a point, that in all the placentas that I have looked at in the last 17 years, to be sure not with the meticulous detail that Dr. Wislocki has looked at them, I have never found any evidence of increment of growth in the cytotrophoblast in the mature or maturing placenta, whether from a normal or toxemic pregnancy. I don't know specifically at what time mitotic activity ceases in this tissue but the amount of cytotrophoblast with respect to the amount of placental tissue seems to coincide very sharply with the peak of the excretion of the chorionic gonadotrophic hormone.

DR. OLIVE SMITH: Except at term.

CHAIRMAN HERTIG: Dr. Wislocki, do you have any specific data on mitotic activity in the cytotrophoblast and when it ceases?

DR. GEORGE B. WISLOCKI: In the literature it is stated by leading authorities that the cytotrophoblast vanishes around the 6th or 7th month. My own impression gained from several placentas studied in the last trimester of pregnancy is that some of the cytotrophoblast persists. In the case of the villi at term there are very occasional cells identifiable as Langhans cells. In regard to the cellular trophoblast of the junctional zone, originally comprising the trophoblastic shell and the trophoblastic cell columns, that also is repre-

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DISCUSSION

CHAIRMAN HERTIG: Dr. Page's paper on an extremely difficult subject is very interesting and provocative.

I would like to cite some data that we have accumulated lately at the Boston Lying-in Hospital, which merely substantiates the general point of view that there is a hypoxia in the toxemias. Dr. Lloyd Sexton, who is here in the room, has done the brunt of the work in gathering these data. He has found that with increasing severity of toxemias there is an increasing severity and increasing incidence of premature separation of the placenta due to the ischemia and breakdown of the decidua with subsequent hemorrhage between the placenta and the myometrium. This results in premature separation of the organ which causes further destruction of the placenta itself. The kind of infarction which occurs in toxemia or tends to occur in toxemia is a very interesting one and is merely a modification of this premature separation process. A small or large localized hemorrhage occurs in the decidua and subsequently breaks through into the placenta leading to ischemic necrosis of the placenta. It is our experience that there is no significant increase in the intervillous thrombosis type of so-called infarct in toxemia as compared to the incidence of the same variety of thrombosis in the placenta of normal pregnancy.

This paper is now open for general discussion. The Drs. Smith's names have been mentioned and I should like to call on Dr. Olive Smith to say something about the nature and the effect of menstrual toxin, which is similar to or identical with necrosin.

DR. OLIVE SMITH: There were a number of things that came to Dr. George Smith's and my mind in the course of Dr. Page's very excellent and stimulating talk, aside from his references to our menstrual toxin, which, as he has rightly stated, has not been identified. We don't know what it is and it probably will be a long time before we find out, partly because of its marked lability and partly because protein chemistry is a field in which progress is not rapid. However, we are working on it.

In his list of conditions that could result in placental ischemia, he left out, to our minds, one very important one, namely, hormonal deficiency. We know that the combined action of estrogen and progesterone typically causes increased vascularity as well as growth of the uterus. In the pregnant uterus, this must be of primary importance in the maintenance of proper blood supply to the placenta. We also know that withdrawal of hormonal support from the uterus, whether it is in the pregnant or non-pregnant individual, is inevitably followed by vasoconstriction and ischemia.

There are, of course, a great many other conditions that may result in intra-uterine ischemia. These have been listed by Dr. Page and undoubtedly are involved in the primary etiology of pre-eclampsia in the majority of cases. Our studies have shown, however, that decreased blood supply to the placenta results in a decrease in the secretory activity of this organ so far as estrogen and progesterone are concerned. Whatever the primary etiology, therefore, the final syndrome is the same, a vicious circle in which vascular and hormonal deficiency are augmenting one another. We would add to this vicious circle the toxic factor that appears to be released in any situation involving tissue breakdown, our so-called "menstrual" toxin, or perhaps it should be called "catatoxin," since it is probably a product

from consideration, because in such cases the decidua is supposed to be absent or scantily developed.

DR. OLIVE SMITH: We have studied 1 case quite recently where an Rh-negative patient had a stillbirth and 3 previous pregnancies. The Rh business was not discovered until this pregnancy. We did not know about the Rh-negativity when we started our studies on her. She had fetal death in utero in the 29th week. We were not following the chorionic gonadotrophin but in all the studies we have done so far the gonadotrophin and pregnanediol excretion bear an inverse ratio to each other, and as Dr. Page suggested, this patient showed exactly the same picture that we get in any other patient who has stillbirth toxemia or premature delivery. There was a progressive decrease in pregnanediol excretion for some 6 weeks before the intra-uterine death occurred. That of course has been our thesis from the start, that any number of things could be primarily responsible for this steroid deficiency, but the final syndrome always includes the steroid deficiency, and if we can fight the steroid deficiency perhaps we can do something about the final syndrome.

CHAIRMAN HERTIG: Thank you! Dr. Dieckmann's name has been mentioned by the essayist. Would he care to comment?

DR. WILLIAM J. DIECKMANN: Dr. Page has given us a very interesting theory of eclampsia. I do not believe it to be as simple as his explanation would seem to indicate. Some twenty years ago when I was repeating Obata's work, I thought enzymes might be the cause but I have since changed my mind. However, I wish him luck in his study of these enzymes.

I was quite pleased to hear him state that the increase in blood pressure (hypertension) is a compensatory phenomenon. There has been far too much investigative work based on the theory that preeclampsia-eclampsia is primarily an increase in the blood pressure. I believe most evidence indicates that the condition is primarily a water and salt retention. Unpublished work of ours indicates that there are also secondary factors.

I wish to ask him if he has any respiratory quotients on tissue from hydatidiform moles. Patients with these moles have the highest incidence of preeclampsia.

He did not state anything about erythroblastosis but since the discussion is informal, for general information I wish to state that we have not found any increase of preeclampsia in patients who have had the special blood groups necessary for erythroblastosis to develop.

DR. PAGE: Thank you, Doctor Dieckmann. It was not my intent to suggest that an increased incidence of toxemias might be found in connection with erythroblastosis. The syncytium itself is in good condition in such cases, and one might anticipate that perhaps the only disturbance would be a disproportionate increase in the chorionic gonadotrophin level.

We have not had the opportunity to make any measurements of the oxygen consumption of fresh hydatid mole tissue.

The liver biopsy studies that I referred to were those of Ingerslev and Teilum, who found that only those women with moderate or severe grades of pre-eclampsia showed extensive fibrin deposition during life.

As long as we are speculating, we might suggest that perhaps the activation of plasminogen, the precursor of the fibrinolytic enzyme, might be related in some way to this whole mechanism of fibrin deposition and fibrinolysis, when this occurs in the body.

CHAIRMAN HERTIG: If I may take one more moment to answer Dr. Dieckmann's question about the type of lesion in the severe pre-eclamptic, we once saw a patient who had severe pre-eclampsia who was recovering and clinically was essentially normal. She suddenly developed pulmonary edema and died within ten minutes. She had a very interesting liver lesion, which was not associated with fibrin deposition but with a triangular infarctive type of fragmentation of liver columns which followed very accurately the distribution of a small hepatic arteriole which could have been in spasm.

DR. JOHN P. PETERS: I don't belong to the fraternity that is talking here today so I should be a little careful. I am not quite an amateur, but I have found that I don't know much of the nomenclature, and there are lots of passwords that I apparently must learn before I can be formally accepted into the organization. On the other hand, as an amateur

sented at term by residual cells definitely recognizable in sections. Between 8 and 9 months, searching the very base of the placenta, one comes across small islets consisting of half a dozen or a dozen viable looking cells. Similarly in occasional cell islands encountered in the placental labyrinth at term one comes across clusters of perfectly viable trophoblastic cells. Consequently, upon careful examination, cellular trophoblast is found right up to term. This residual cytotrophoblast could explain the occurrence of the chorionic gonadotrophin at the end of pregnancy.

To what extent these cells might multiply is a different matter. I have not examined any eclamptic or toxemic placentas critically enough to know whether or not these clusters of cells are diminished or increased. Since they look viable and their nuclei are intact, I see no reason why they might not be capable of dividing mitotically. Whether they actually do so under any conditions I do not know.

CHAIRMAN HERTIG: Thank you, Dr. Wislocki.

I would agree with everything Dr. Wislocki has said regarding the persistence of cytotrophoblast. It does look viable but we find that it apparently does not grow at any stage in pregnancy beyond approximately the first trimester. Furthermore there appears to be no correlation between the amounts and quality of cytotrophoblast and the presence or absence of clinical toxemia.

We have undertaken, in conjunction with the Drs. Smith, to study some of the placentas of their patients who have been given stilbestrol. Their study group includes normal patients as well as toxemic patients. We have attempted in a preliminary way to do some histochemical studies on them with respect to acid and alkaline phosphatase, and with sudan black. We are not the masters at it that your first essayist is and we have, in the course of a very limited investigation covering 4 toxemic placentas and some 7 or 8 non-toxemic placentas been unable to show any changes in the cytotrophoblast which could be correlated with the administration of stilbestrol.

Dr. Page, would you care to say anything at this point before the final discussion with respect to what has been said thus far?

DR. ERNEST W. PAGE: I am happy that Doctors George and Olive Smith contributed their views, and I think that they are very likely to be correct. I was simply placing the steroid deficiency as the cart behind the horse, laying emphasis on the primacy of the circulatory mechanism, with a disturbance of steroid production being secondary. It is quite possible, of course, that once a steroid deficiency exists, there might be a vicious circle as suggested.

My suggestion that an increased chorionic gonadotrophin at term or in the toxemias may be a reflection of some mitotic division on the part of the cytotrophoblast was perhaps premature. I think Dr. Wislocki answered the question in part when he said that the potentialities for such division do exist and that it would be extremely difficult to determine this by any quantitative histologic study.

Along that line, I am wondering if the so-called persistence of the cytotrophoblast at term in such placentas as those accompanying erythroblastosis may not have some bearing on this problem. We have seen cases in which we are quite sure that damage to the placenta does not begin until seven and one-half or eight months, because that may be when Rh antibodies first appear. At this time, the Langhan's cells have allegedly disappeared, and yet these placentas, so I am told, show a "persistence" of the cytotrophoblast at term. Could it not be that they actually multiplied after the Rh antibodies appeared? It occurred to me that it might be exceedingly interesting to follow the chorionic gonadotrophin level in the blood of those patients developing Rh antibodies in order to see if the same type of hormonal imbalance might not occur under those circumstances. If it does, then we might say that here is an example where the hormonal imbalance is simply a reflection of the ratio between cytotrophoblast and syncytium.

In regard to Dr. George Smith's comment, I might have been in error in not considering the decidua as well as the trophoblast. The fact that typical eclampsia has been reported in association with abdominal pregnancies may have influenced me in omitting the decidua

PATTERNS OF UTERINE CONTRACTILITY
IN WOMEN DURING PREGNANCY*

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INTRODUCTION

The complications of labor can be clarified by a more thorough understanding of the patterns of normal and abnormal uterine contractions. At present, we are in the dark concerning many of these despite serious study for many years. Today, we are going to present results obtained with a new method by means of which these patterns of uterine contractility may be determined objectively. In this connection, the most significant point which we would like to make is the following:

To dilate the cervix, intermittent contractions in the fundus must be strong, they must rise quickly to a maximum, and they must be of relatively long duration. In contrast, in the mid-portion of the uterus the contractions are less intense, they are usually shorter in duration and they frequently diminish progressively in force as labor advances. The lower uterine segment is inactive throughout the first stage of labor. Thus we see that *cervical dilatation is the result of a gradient of diminishing physiological activity from the fundus to the lower uterine segment.* We also see that the functional components of this activity are the *intensity* and the *duration* of the contractions. In uterine inertia as well as in the other uterine dyskinesias during labor, the contraction pattern in the uterus deviates from this simple, effective pattern. On what grounds is this statement made?

The foregoing statement is based upon our current studies. These are being made with an instrument operating on a principle never heretofore employed in human tokography. The research program is continuing daily through the joint efforts of the Department of Obstetrics of the Johns Hopkins Hospital and the Department of Embryology of the Carnegie Institution of Washington. It is so organized that as every new record is obtained it is analyzed and coded and these data, along with pertinent clinical data, are entered on punch cards for eventual statistical analysis. As months go by, therefore, conclusions which we have reached today, based upon some six dozen records obtained since September 1947, will undergo revision. Certainly they will acquire a quantitative aspect which is now lacking as a result of the extended statistical study on which we are just now well embarked. What we have to offer today, therefore, is a considered evaluation of a variety of patterns of uterine activity which we have seen repeatedly in the several clinical courses of labor to be described below.

I have a slight advantage, and you have too, because anything I say may be considered utterly irrelevant.

I can not help wondering what to say when a paper is presented as speculation. Such a presentation is completely disarming; one can not criticize speculation. I can not help feeling that no disease can be studied in vacuo. I can not refrain, therefore, from citing some other amateurs that seem to have been neglected here. Emily Loeb and Beatrice Seegal have shown that a nephrotoxic nephritis can be produced by placental tissue. This seems to me a very significant thing, but one that was not mentioned in relation to the placental origin of toxemias.

This has other implications. Initially I embarked on the study of toxemias because of my great interest in acute nephritis, because it seemed to me that I might find in toxemias, and especially in the types that were just discussed, the eclamptic toxemias, something I have looked for all my life, the death of a patient with acute nephritis through some incidental cause, in this case pregnancy. The pictures of toxemia and acute nephritis are not very different. It is not, therefore, insignificant that a nephrotoxic nephritis can be produced by placental tissue and by no other tissues except the kidneys.

The analogy to nephritis is too close to allow all the data that have been accumulated in the study of nephritis to be neglected in the consideration of toxemias. What propriety is there in treating eclampsia as if it were a thing apart? It is defined in the dictionary as flashes before the eyes, convulsions or some kind of explosive seizures. When these are encountered in the course of a nephritis which has been attended by edema and hypertension, we do not speak of them as a different disease, having a different origin. We consider them as episodes in the disease. I can see no reason to adopt a different attitude towards eclampsia. The circulatory factors which precipitate convulsions in nephritis are to me, an amateur, relevant to the subject of eclampsia in which the same circulatory disorders occur.

We have just heard that in this disease there are liver lesions which can be demonstrated by biopsy only in the most severe cases. At post mortem they were not common in either Bell's series or my own—because I have investigated the pathology of the condition to some extent. To consider that these lesions in any case are pathognomonic of or directly related to eclampsia seems to me an odd conceit. When women die in eclampsia they die, in ordinary medical terms, of shock with heart failure. I know no condition in which the liver is more seriously damaged. Why then should these lesions in the liver be attributed to specific disorders when the same kinds of lesions are encountered in other patients that die with this syndrome. They are part of the syndrome. There are many phenomena that are described as if they were peculiar to eclampsia which might better be considered as the results of convulsions or the circulatory disturbance which precipitated the convulsions.

I make the plea that the field of adventure be enlarged. While some of us are approaching the subject from internal medicine, you who are in the fraternity should also seek analogies. The phenomena you encounter are not confined to eclampsia; their causes may be the same in toxemias as in the other conditions in which they occur.

One more remark I can not help making. The teleological explanation of hypertension of pregnancy suggested by the speaker has been suggested in nephritis and in other types of hypertension. The suggestion has not proved fruitful in these latter conditions and there is no reason to believe that it will be in the toxemias.

CHAIRMAN HERTIG: Thank you, Dr. Peters! I can only say I have seen a good many dead eclamptics and none of their livers looked alike. They vary all the way from isolated necrotic cells to massive infarction of the liver, so that I would agree with Dr. Peters that there is not anything particularly pathognomonic about the liver lesion in eclampsia, except that it is damaged.

The reason for subsidence of activity in this part of the uterus is clear from examination of many of the individual contractions taking place in the fundus and mid-zone of the uterus simultaneously. In nearly all cases, both reach a maximum at the same time. The fundus remains contracted much longer than does the mid-zone, however. The duration of the contractions in the fundus in
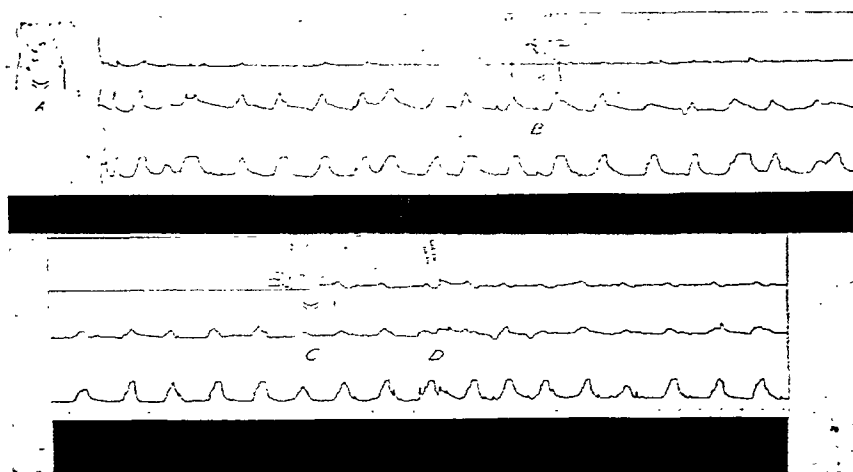
FIG. 1. Record from early part of first stage of labor in a primigravida with a spontaneous delivery. Fundus (area B) bottom: mid-uterus (area E) middle; lower uterine segment (area H), top.
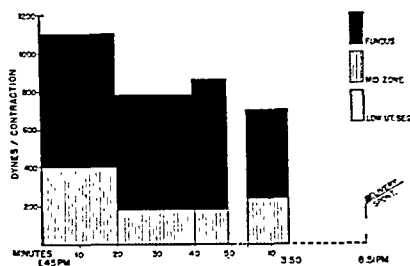
FIG. 2. *Work* in different parts of uterus, from record shown in Figure 1. Dynes per average contraction for different periods of time, as indicated. Determined by planimetric determinations of areas under contraction curves.

this record frequently outlasts by thirty seconds or more those of the mid-zone. Clearly, the fundus exerts considerable force upon the more caudal parts of the uterus.

This record has been analyzed with several interesting results that bear out the foregoing statement. Figure 2 shows, for example, the excess of work, in dynes per average contraction, in the fundus as compared to the mid-zone of the uterus for the periods of time indicated in the graph. The lower uterine segment, it should be noted, did no measurable work.

THE STRAIN GAGE MULTI-CHANNEL TOKODYNAMOMETER

The instrument which we are using to study the pattern of uterine contractions is a strain gage multi-channel tokodynamometer. It is multi-channel because the contraction characteristics are recorded from three uterine zones simultaneously. Usually these locations are in the fundus, in the mid-zone of the uterus, and in the lower uterine segment.

The unit employs three resistance strain-gages as the active elements by which the mechanical action of the uterus is made to alter the resistance to current-flow in each circuit by means of levers. These apply strain to the elements of the gages in proportion to the local force of the uterine contraction. The record is obtained electrometrically in a frictionless system in which the three channels record with a series of fine holes on heat-sensitive paper by means of a sparking device on the end of each electrometer needle. The unit is called a tokodynamometer by virtue of the fact that it measures forces pertaining to birth. For simplicity, the tokodynamometer is referred to as a TKD.

A preliminary note describing the unit was published in Science for 31 October 1947, (Reynolds, Heard and Bruns, 1947) and a detailed account of it is about to be published in the Bulletin of the Johns Hopkins Hospital (Reynolds, Heard, Bruns and Hellman, 1948). Consequently, the technical aspects of the construction and operation of the TKD need not be described at this time.

Most of the previous methods of tokography have measured uterine contractions in one of two ways. In one, the expulsive force of uterine contractions is measured by a special spring-containing forceps (Joulin, 1867; Kristeller, 1861) or by a balloon placed in the lower uterine segment during the first stage of labor (Schatz, 1872; Rucker, 1930; Woodbury, Hamilton and Torpin, 1937). In the other method, various devices have been placed upon the ventral abdomen, and uterine activity from a single point has been recorded. These instruments have ranged from a simple weight put on the abdomen and connected to a kymograph (Rübsamen and Gusikoff, 1920), to a variety of units applied to the abdomen and recording on a paper, kymograph or gage (Credé, 1861; Crodel, 1930; Dodek, 1932; Antoine, 1935; Deffner, 1932; Murphy, 1946). All of these methods have in common the fact that they record from only one point on the abdomen and they record the total shift in shape and position of the uterus with each contraction.

In contrast to the above, the TKD records from three points simultaneously. At each point it measures the force required to change the shape of the uterus locally, under the brass mounting of the strain gage. Consequently, the strength and temporal relations of activity in different parts of the uterus may be compared with each other. This feature affords information, therefore, concerning the origin, spread, and dissipation of the wave of contraction over the surface of the uterus.

The recording by sparks at half-second intervals provides a uniquely desirable feature for this work. If the fetus kicks or moves, the needle is deflected for a second or less, and only one or two sparks are made to one side of the main line of sparks which comprise the uterine tracing. As a result, such artifacts do not show on the records.

PATTERNS OF UTERINE CONTRACTIONS

Spontaneous onset of labor with spontaneous delivery in a primigravida. A typical record of the activity associated with the first stage of normal labor is shown in Figure 1. This is one of the earlier records in which activity in the fundus of the uterus was recorded at the bottom of the paper, contractions from the mid-zone in the middle tracing, and contractions in the lower uterine segment were recorded at the top.

This TKD is noteworthy for several reasons. Its most conspicuous feature is the *subsidence* of activity in the mid-zone of the uterus. This is a common finding in many records in which cervical dilatation proceeds rapidly.
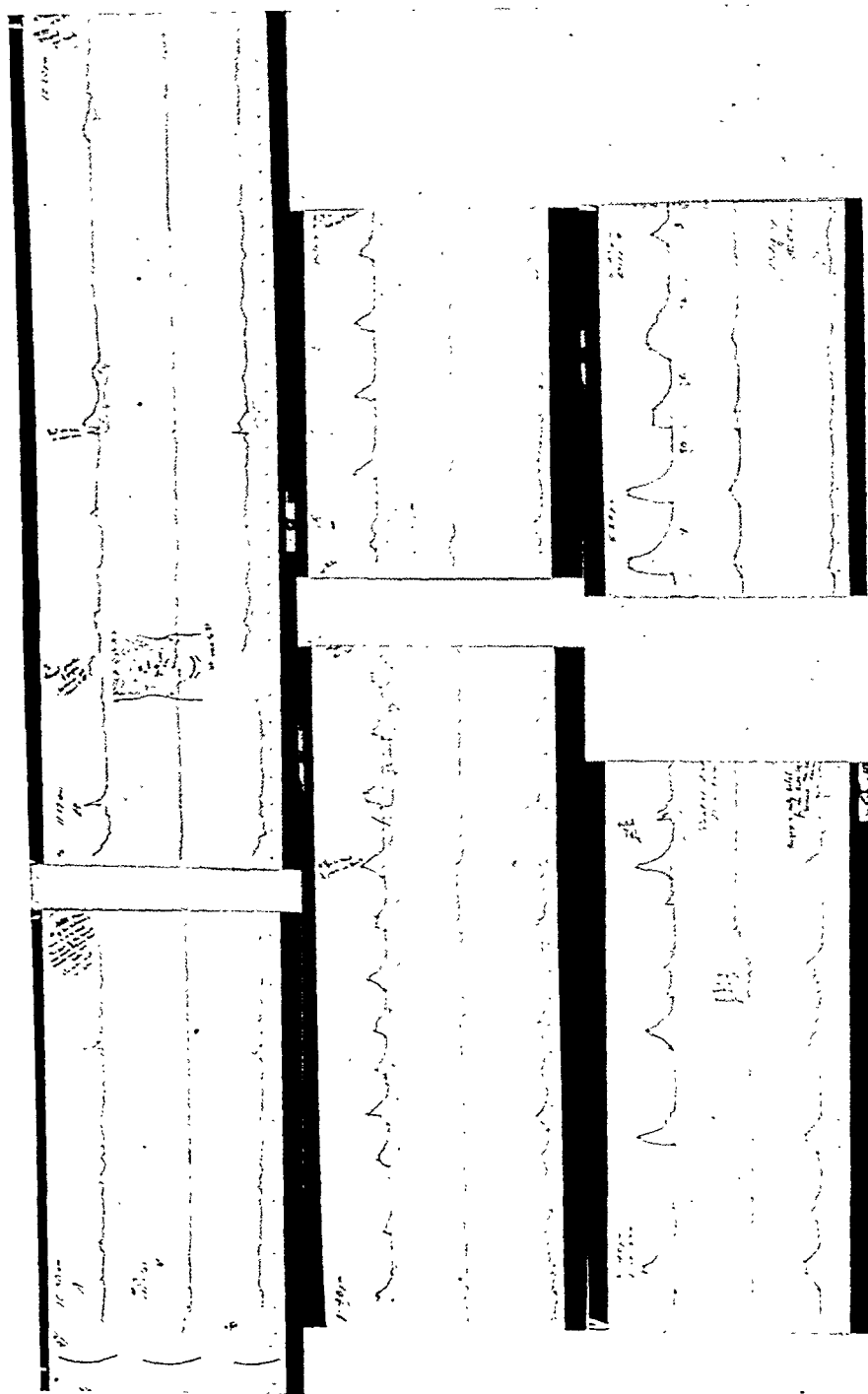
Fig. 7. Induced labor in a primigravida. No contractions recorded during a fifteen minute control period prior to rupture of the membranes.

How is the extra work accomplished by the fundus? It is achieved in two ways. Figure 3 shows the intensity of the average contractions, expressed in grams per contraction against the plunger in the center of the brass ring. The areas of the rings are the same for all three leads. The contraction characteristics of each may be compared with each other, accordingly. Throughout the entire period of recording, the *intensity* of contractions in the fundus exceeds that in the mid-zone. Figure 4 shows that the duration of the contractions in the fundus likewise exceeds those in the mid-zone of the uterus. The first stage of labor
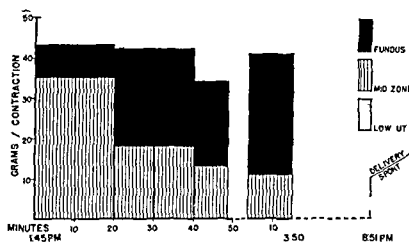
FIG. 3
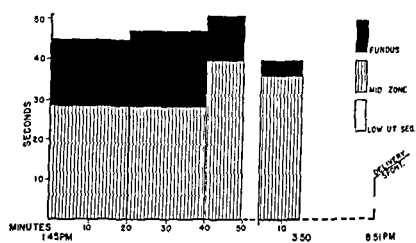
FIG. 4

FIG. 3. Intensity contractions (grams force per average contraction) in different parts of the uterus, from record shown in Figure 1.

FIG. 4. Duration of contractions (excluding relaxation phases) in different parts of uterus, from record shown in Figure 1. Note that the contractions in the fundus outlast those in the rest of the uterus. See text for discussion.

FIG. 5

FIG. 6

FIG. 5. Intensity of contractions in different parts of the uterus in the record from a spontaneous delivery in a multiparous woman.

FIG. 6. Duration of the contraction phase of average uterine contractions in different parts of the uterus of a multiparous woman. Same record shown in Figure 5.

advances accordingly, because the work of the fundus exceeds that of any other part of the uterus. Its activity is maintained, in fact, while the rest of the uterus becomes increasingly inactive, or passive. The lower uterine segment is susceptible to progressive dilatation by virtue of the continuing work of the fundus throughout the first stage of labor which exceeds that in the rest of the uterus.

Spontaneous onset of labor, operative delivery, multipara. A number of recordings have been obtained from multiparous women. These have shown some variation with regard to the work of the fundus relative to the remainder of the uterus, but in general, the earlier phases of the first stage of labor are characterized by little activity throughout the uterus except in the fundus.

the recording at 6:00 p.m. This was two hours before operative delivery by the use of prophylactic low forceps and episiotomy (see Figures 8 and 9).

The record clearly shows, in this induced labor, as in the case of the preceding patterns, that the progress of the first stage of labor depends upon the establishment within the uterus of a physiological gradient in which the fundus dominates the rest of the uterus with respect to the intensity, duration, and hence the work of the uterine contractions.
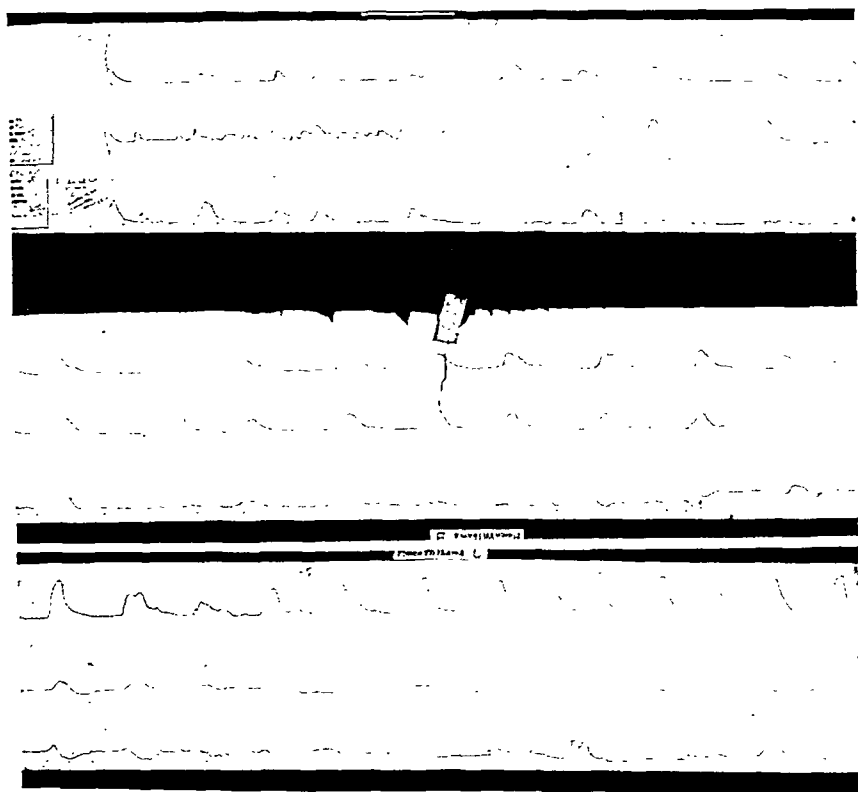
FIG. 10. Record of premature labor (duration of pregnancy, 31 weeks). Note subsidence of activity in lower uterine segment, and development of expulsive pattern of contraction involving strong contractions in the fundus.

Premature labor. Uterine tracings with the TKD have been obtained throughout most of one premature labor. In this, the weight of the child was 1560 grams, and the duration of pregnancy was about thirty-one weeks.

The patient developed painful uterine contractions after rupture of the membranes about 8:00 a.m. The record was begun at 10:35 a.m.

In Figure 10, an interesting trend in the pattern of uterine contractility developed. At first, all three levels (fundus, mid-zone, and lower uterine segment) were active, particularly the lower uterine segment. The mid-zone at the be-

In one record, only the fundus exhibited activity during the period of observation. Figures 5 and 6 demonstrate this graphically in terms of a) *intensity* of the average contractions and b) *duration* of the contraction phase of each contraction, respectively. Clearly, the work of the uterus during the first stage of labor in this instance was associated with no opposing contractile force. It therefore follows that the first stage of this labor was facilitated by virtue of the fact that the work of the uterus was restricted to one end only and that, the fundus. Any deviation from this pattern should prolong the first stage of labor.

Onset of the second stage of labor. When full cervical dilatation is accomplished, a characteristic change in the TKG may be observed. The lower uterine segment is inactive throughout the first stage of labor. At the moment of complete cervical dilatation and coincident with the onset of the second stage of labor, forceful reflex abdominal movements
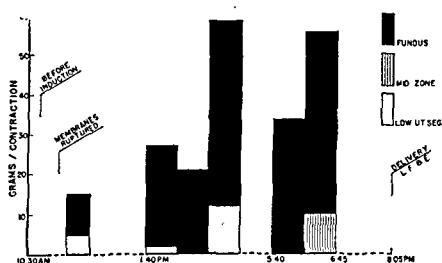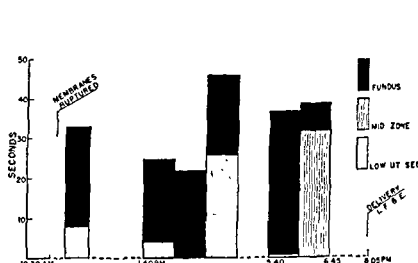
FIG. 8.   FIG. 9.

FIG. 8. Intensity of uterine contractions in induced labor in different segments of the uterus (see Figure 7).

FIG. 9. Duration of contractions in different segments of the uterus in induced labor (see Figure 7).

take place. These give rise to peaked excursions in all three leads which recur with each bearing down movement. The appearance of these stigmata in a record from a patient lying quietly are indicative, therefore, of the fact that dilatation is complete, and that reflex bearing down movements have begun.

Induced labor, primigravida. Only one record of this condition has been recorded by us up to this time. The record includes a preliminary period of observation in a full term primiparous patient. Not a single contraction was recorded throughout the uterus during a fifteen minute period. This is shown in Figure 7.

The onset of activity in the uterus began a short time later. It commenced as feeble activity in the fundus, and in the lower uterine segment as well. Rupture of the membranes occurred at 11:00 a.m. By mid-afternoon, activity became progressively stronger in the fundus; the mid-zone of the uterus remained quiescent, and only very occasionally was a uterine contraction recorded in the lower uterine segment.

The force, regularity, and duration of the contractions in the fundus became greater in the late afternoon. The establishment of this type of activity was associated with rapid dilatation of the cervix which continued until the end of

resistance in all other parts of the uterus owing to the presence of strong contractions throughout, including the lower uterine segment.

A second type of false labor has been observed. In this, the lower uterine segment was inactive throughout the period of observation while the mid-zone

Fig. 13. False labor, with strong contractions throughout the entire uterus, but especially in the lower uterine segment.
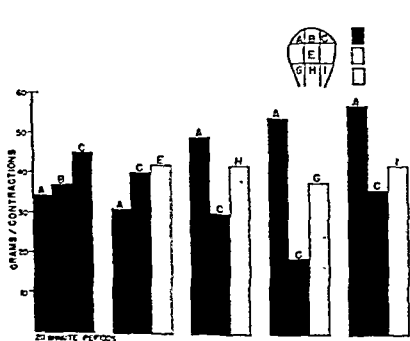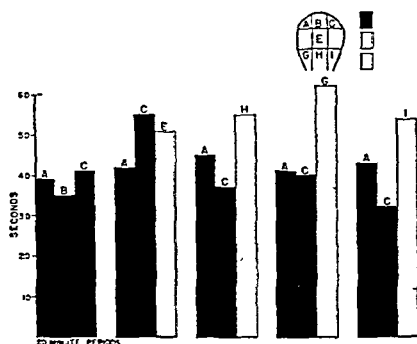
Fig. 14   Fig. 15

Fig. 14. Intensity of contractions in different parts of a uterus in false labor (see Figure 13).

Fig. 15. Duration of contractions in different parts of a uterus in false labor (see Figure 13).

of the uterus contracted with great force. Moreover, the duration of the contractions in the mid-zone of the uterus equaled or exceeded the duration of those in the fundus. In short, what may be called a "physiological contraction ring" developed with each contraction. Hence it is understandable that a true first stage of labor could not progress at this time. This is borne out by the analysis

ginning of the record exhibited highly irregular activity. During this time, the cervix remained at 4 centimeters dilatation. With the passing of time, however, the lower uterine segment became progressively and increasingly inactive, the contractions in the fundus became stronger, and the activity in the mid-zone, while fairly rhythmical, became weaker and weaker. Within a few hours, the pattern was typical of the spontaneous labor described above (see Figure 1), and dilatation of the cervix was progressive and rapid until the onset of the second stage of labor at 2:15 p.m. Delivery occurred at 2:55 p.m. (See Figures 11 and 12 for the analysis of this record.)

In this instance, as in the others above, one witnesses again the fact that progress in the first stage of labor is dependent upon the establishment of a gradient of motility in which the fundus contracts rhythmically and strongly, as the more
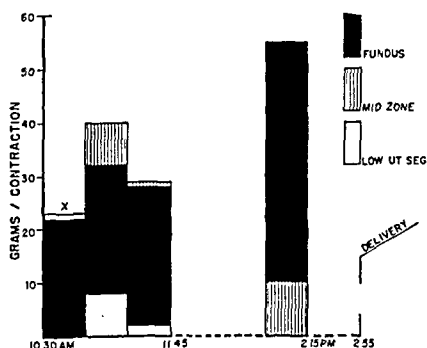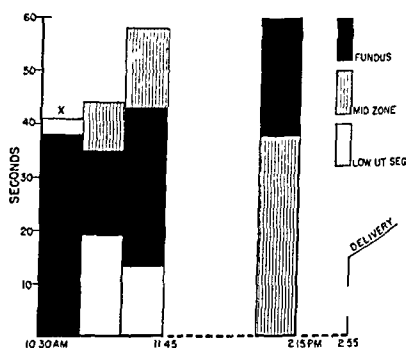
FIG. 11.   FIG. 12

FIG. 11. Intensity of contractions, premature labor. At X, the mid-zone of the uterus was irregularly active, and this activity could not be analyzed. Note diminishing activity, first of the lower uterine segment, then of the mid-uterus, See Figure 10.

FIG. 12. Duration of contractions, premature labor. Analysis of record shown in Figure 10.

caudal portions of the uterus are partly or completely quiescent. In this way, the cervix is effectively dilated.

False labor. No doubt there are a number of patterns of uterine activity in false labor. We have observed three instances, two of which will be described.

Figure 13 shows excerpts from one of the tracings. Here, it will be observed, there were strong contractions throughout the entire uterus, no matter where the gages were placed on the abdomen. There was strong activity even in the lower uterine segment. This is shown by the analysis of this record with respect to the strength and duration of contractions in all parts of the uterus (see Figures 14 and 15). It was variable in the fundus, however, showing a shift in intensity from left to right as the record progressed.

Comparison of the pattern of uterine activity observed in the foregoing instance with the observation in each of the four preceding records shows why this labor was destined to be a false one. The contractions of the fundus encountered

possible to state that entirely new effects of this oxytocic on the gravid uterus can be evaluated. This will be clear from the record shown in Figure 18, and the charts summarizing the analysis of this tracing in Figures 19, 20, and 21.

One half minim of pituitrin was administered intramuscularly three times to a patient who had been in labor more than ten hours, with delay of cervical dilatation at 9 centimeters for more than two hours despite the presence of fairly strong
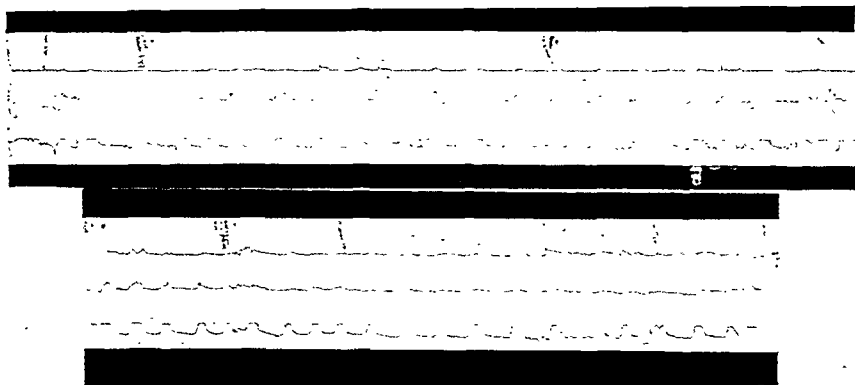
FIG. 18. Effect of intramuscularly administered pituitrin, 0.5 minim per injection. The cervical dilatation stopped two hours at 9 centimeters. Activity recorded at three levels of the uterus. Fundus, bottom; mid-zone, middle; lower uterine segment, top. The record was interrupted after the second injection by a period of nausea and vomiting.
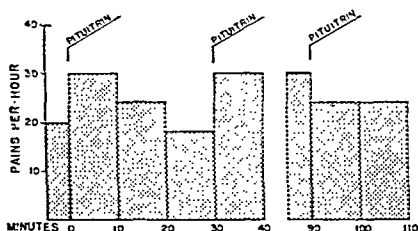
FIG. 19. Frequency of uterine contractions after three pituitrin injections in tracing shown in Figure 18. Note acceleration after the first two injections, but not the last. Dilatation to 10 cm. followed soon after the third injection.

uterine contractions clinically. The second injection was made forty minutes later, and was associated with a period of retching, nausea, and vomiting.

The third injection was made more than an hour later. The first and last responses were entirely dissimilar; the first giving rise to an undesirable therapeutic effect, the last, to a desirable one. These effects are shown in the following analysis.

The *frequency of contractions* increased after the first two injections, and not after the third injection (see Figure 19). This acceleration is the response generally associated with a good pituitrin effect. One might think, therefore, that

which is summarized in Figures 16 and 17. Attention should be drawn to the fact that this labor was particularly painful.

Tracings made on this patient the next day showed that the hyperactivity of the mid-zone of the uterus had subsided, and the activity in the fundus became dominant. The lower uterine segment exhibited contractions, however, although the uterus became inactive by evening. The patient was then sent home. She returned in labor twenty-four hours later, and delivered spontaneously at 11:05 p.m. that night. No record of uterine activity was made at that time.

Uterine inertia. Records of uterine contractility have been obtained in a number of cases of uterine inertia. An extended study of this condition will be made. It appears that there is no simple or consistent pattern of activity in this entity owing, no doubt, to the diverse factors contributing to it.

In one case in which labor had lasted twenty-six hours, there had been activity in all three leads of the record. This suggests the reason for the prolongation of labor: the lower uterine segment offered contractile resistance to the work of the fundus. A record made
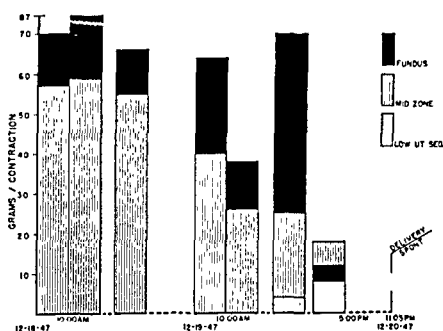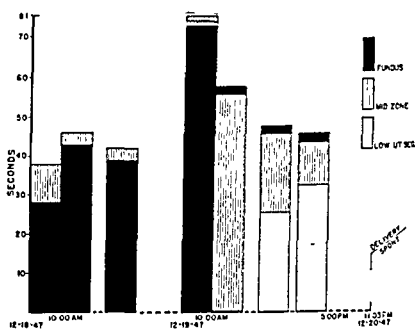
FIG. 16   FIG. 17

FIG. 16. Analysis of record from a second type of false labor. Middle of uterus is hyperactive. Intensity of contractions in different parts of uterus.

FIG. 17. Duration of contractions in record shown in Figure 16 (false labor).

two hours later and just one hour before spontaneous delivery showed the characteristically effective pattern of strong contractions in the fundus only.

Another patient, gravida ix, had been in labor for thirty-six hours. In this record, the fundus was most active, and the rest of the uterus was relatively inactive. According to current experience with normal labors, this should have been a most effective pattern of activity for dilating the cervix, particularly in a multiparous woman. However, the fetus presented by breech and weighed 3970 grams. Delivery was eventually accomplished by cesarean section. This case is classified as one of uterine inertia. It appears from the clinical record that failure of the cervix to dilate was due in part at least to poor apposition of the large breech to the cervix. In this way, the force of the contractions in the fundus would be dissipated and rendered ineffective in dilating the cervix.

Effects of pituitrin. Whenever a new method of recording uterine activity is devised, it is almost inevitable that it will be used to test the effect of pituitrin. In a sense, this is really a test of the method since the effects of this drug are considered to be generally well-known. With the tokodynamometer, however, it is
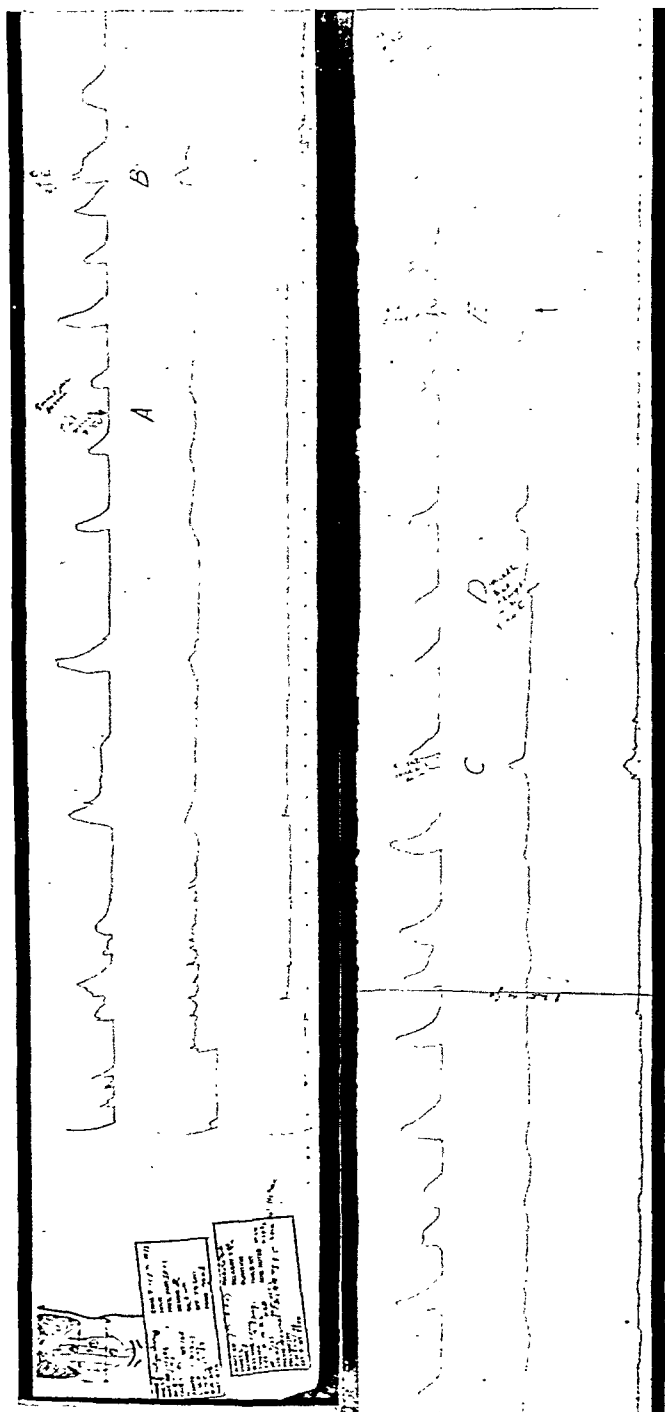
FIG. 22. Effect of intravenously administered pituitrin, 0.5 minim per half hour by drip. Note that pituitrin augmented activity only where it existed prior to the injection. A, pituitrin started; B, cervix 3 centimeters; C, rectal palpation; D, middle lead position changed; E, pituitrin stopped.

judging from the frequency response, the first two injections were effective, whereas the last injection was ineffective.   Other considerations lead to an opposite conclusion, however.

The *intensity* of the contractions in the fundus and the mid-zone of the uterus is shown in Figure 20.   Here it will be seen that the intensity of contractions in the mid-zone of the uterus increased, so that they actually became stronger than in the fundus during the second and third ten minute periods following the injection.   In short, a "contraction ring" or hour glass uterus developed with each contraction.   The third injection of pituitrin had no such effect.   For a reason which will be explained below, the intensity of contractions in the fundus became greater, and those in the mid-zone of the uterus diminished markedly.   This difference in activity between the fundus and the rest of the uterus is, as we have seen, a prerequisite for cervical dilatation.   In this case, the cervix did dilate
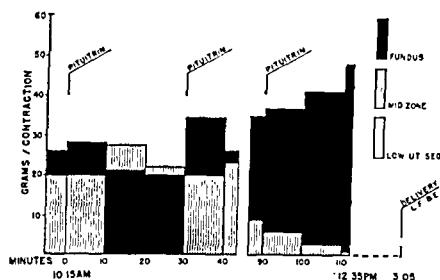
FIG. 20   FIG. 21

FIG. 20. Intensity of uterine contractions at different levels after pituitrin administered as shown in Figure 18.   Note that the mid-zone of the uterus responded more strongly than did the fundus after the first injection.
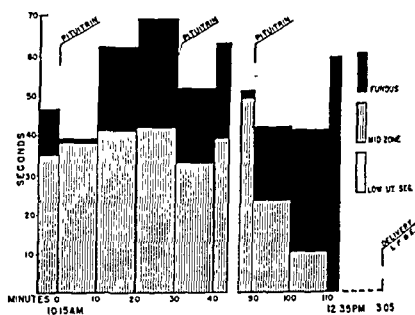
FIG. 21. Duration of contractions at different levels after pituitrin administered as shown in Figure 21.   Note that for a time after the first injection the midzone of the uterus contracted for a longer time after the pituitrin.

fully.   After a second stage of labor lasting two and one half hours delivery of a living child was accomplished with low forceps and episiotomy.

The reason for the different pituitrin effects just described may be in part attributable to the fact that the duration of the contractions in the mid-zone of the uterus increased during the first ten minute period after the first injection. No such effect followed the last injection.   This is shown in Figure 21.   It seems safe to conclude that the reason for the prolonged first stage of labor in this case was the result of a hyperactive and hyperirritable mid-segment of the uterus. The injection of pituitrin at first accentuated this effect with the results seen above.   When, however, the gradient of activity became reversed and normal, the third injection of pituitrin served to advance the labor in an effective manner.

A number of other records of the effect of pituitrin have been obtained.   In some, this drug was administered by intravenous drip, at the rate of 0.5 unit per half hour.   An example of this is shown in Figure 22.   Here, it will be seen,

In the first stage of labor, the contraction of the muscular walls of the uterus compresses its liquid contents, and the membranes are pushed into the cervical canal, bulging out into the segment of a sphere, and are in most cases eventually ruptured by the pressure of the liquor amnii contained in them.

It is evident from the form of the gravid uterus in Figure 23, that its *curvature* is *greatest* (i.e., the radius is smallest) near its mouth and it is *least* (i.e., the radius is greatest) in the fundus.   Observation shows, according to Haughton, that the proportion of the radii of curvature of the fundus and the lower uterine segment is of the order of 7:4.   The equation cited above shows that the tensile strain, T, is proportional to the product of the principal radii of curvature at any point under consideration.   The difference in tension is of the order of $7^2:4^2$ or $49:16$ or $3:1$.   *Hence the strain is necessarily greatest at the fundus of the uterus and least at the os uteri.*

Normally, therefore, a difference of tension exists between the tissues of the
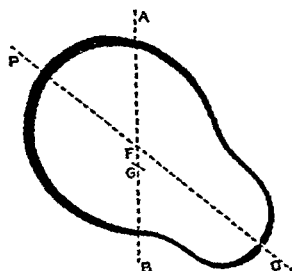
FIG. 23. Natural position and curvature of the uterus (sagittal section) at term.   Note that the fundus and the lower uterine segment form segments of two approximate spheres. OP, axis of uterus; G, center of gravity; F, center of flotation of fetus.   See text for evaluation of relative tensions in the fundus and lower uterine segments from data pertaining to the curvatures of the uterus.   After Haughton.

fundus and the cervix.   This fact, appreciated so long ago by Haughton, has been overlooked by obstetricians and physiologists, yet it is without doubt the key to the results we have presented today.   Not only is the initial *tension* at the beginning of a uterine contraction greater in the tissues of the fundus than elsewhere in the uterus, but the musculature is thicker there, also.   This, as Haughton makes clear, is related to the fact that the force which a muscle can develop is proportional to its thickness.   Thus we see that there is indeed a rational basis for our observations that rhythmic contractions in the uterus at term give rise in normal circumstances to a situation in which the work of the fundus dominates, hence overcomes, that in the remainder of the uterus.

Before concluding this discussion, it is pertinent to discuss briefly the concomitant physiological conditions and sequelae of rupture of the membranes upon the course of labor.   It is generally known that this frequently initiates or accelerates labor.   This is true both for artificial and spontaneous rupture of the membranes.

The essential hydrostatic conditions in the fundus and the lower uterine segment of the uterus at term or in labor have been stated in approximate terms

there was an acceleration in the frequency of contractions soon after the injection was begun, without an alteration in the fundamental normal pattern of activity. In other words, the pituitrin served only to augment existing motility, rather than to initiate it. This is the same effect that was found *in vivo* in the rabbit a number of years ago (Reynolds, 1930). Upon withdrawal of the pituitrin, the activity of the uterus subsided somewhat and promptly upon resumption of pituitrin at a later time, activity favorable for dilatation of the cervix resulted.

Without the use of a multi-channel tokodynamometer, it is clear to us that evaluation of these effects of pituitrin would be difficult or impossible to make. It would of necessity have to rest upon an empirical evaluation of the clinical results obtained.

DISCUSSION

One aspect of the results just described stands out above all others. That is that cervical dilatation has been observed only in the presence of a preponderance of rhythmic activity in the fundus over the rest of the uterus. Occasionally, however, this type of activity is present and cervical dilatation fails to take place owing to faulty presentation or lack of cervical effacement. Thus we observed it in uterine inertia in a multiparous woman, and briefly at the end of a period of false labor in the eighth month of pregnancy. The significant fact which we would stress on the basis of the results today, however, is that no other pattern of uterine activity in labor has been observed which effectively advances the first stage of labor. What, one asks, is the physiological basis for the dominance of the fundus in normal labor?

The answer to this question is provided in a long-forgotten theoretical discussion entitled, *On the Mechanical Forces Employed in Parturition* in *Principles of Animal Mechanics* by the Reverend Samuel Haughton (1873). No word remains concerning how good a minister this Irish divine may have been, but this book bears eloquent testimony to his powers as a mathematician and theoretical physiologist. The argument which follows in abbreviated form is based largely upon his arguments relative to the first stage of labor.

The mechanical problem to be solved for the uterus in labor is one of equilibrium of a flexible membrane subject to the action of given forces, as defined by Lagrange in his *Mécanique Analytique*. The theorem, in general leads to the conclusion that in a sphere $T = \dfrac{pr^2}{2}$ when T denotes the tensile strain acting in the tangential plane of the membrane tending to rupture a band of the membrane one inch broad; p denotes the pressure resulting from all the forces in action, perpendicular to the surface of the membrane and acting on a surface of one square inch; and r is the radius of curvature of the membrane at the point considered when the curvature is spherical.

In the case of the uterus and its membranes, the force p arises largely from the hydrostatic pressure and is therefore easily measured, and the supposition of spherical curvature is approximately admissible. The natural position of the gravid uterus is shown in Figure 23.

force of contractions in the fundus relative to that in the lower uterine segment and in the cervix.

4. The effect of rupture of the membranes (spontaneous or artificial) is shown to be such that, although the absolute tissue tensions diminish somewhat, the net effect is to increase the tension within the fundus relative to what it is in the lower uterine segment. If other conditions are satisfied, the delicate balance of forces which is preventing the emptying by the uterus of its contents is tipped suddenly in the direction of their prompt delivery, and the normal pattern of uterine contractions for effective dilatation of the cervix is favored.

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DISCUSSION

DR. EASTMAN: From a clinical viewpoint, it is our hope that this work of Dr. Reynolds will lead to a better understanding of uterine inertia which we all know is one of the most common and troublesome complications of labor. On the basis of following his work carefully over the months it is my impression that there is some basis for that hope.

We have with us, however, this morning, Mr. Chairman, one of our leading students of uterine motility over the years, Dr. Douglas Murphy, and if anyone should discuss this paper I think it should be he.

DR. DOUGLAS MURPHY: I am very much interested in Dr. Reynolds' paper because we have made some observations upon uterine contractility in Philadelphia.

There are three clinical problems upon which we need information. One of these is the problem of false labor. About 10 per cent of patients experience it.

In some instances we have been unable to distinguish between the contraction patterns of false and true labor using the Lorand tocograph.

A second problem in the field of uterine motility is the question of why the cervix of certain individuals does not open readily. Perhaps Dr. Reynolds' device will help us to answer this question.

The third question is that of uterine inertia. Can Dr. Reynolds give us more information upon the contraction pattern which is found in cases of uterine inertia? I did not observe in his tracings of patients with uterine inertia the characteristics which I have seen, namely, the fact that succeeding contractions rarely resemble each other. Also, we find in the patient with inertia, very small contractions. In cases of inertia, then, we have two particular

above: the *tension* in the two parts is of the order of 49:16 or about 3:1 and the ratio of their *radii of curvature* is 7:4. When the volume of the uterus is reduced a small amount (say by 100 cubic centimeters of fluid) the pressure throughout the uterus is essentially unchanged, since this depends largely upon the hydrostatic pressure of the contents, and the volume is changed only from, say, 3500 to 3400 cubic centimeters. The radii in the several parts of the uterus diminish proportionately as a function of their *cube roots*, since the volume, $V = \dfrac{4\pi r^3}{3}$ in a sphere.

If, therefore, we take the cube roots of 7 and of 4 respectively, we find that they are 1.92 and 1.58. The relative change in the two radii of curvature, therefore, is in the proportion of 1.92:1.58. Accordingly, the effect of this is to reduce each radius of curvature by nearly the same absolute amount, yet 1.92 is a smaller proportion of 7 than 1.58 is of 4 (about $\frac{1}{4}$ and $\frac{1}{3}$ respectively). It is therefore clear that since the tension is a function of the square of the radius, the net effect of removal of fluid from the uterus at term is to *increase the existing difference in tension* between the fundus and the lower uterine segment respectively. For example, if the reduction in the radii of curvature cited above were actually 1.92 and 1.58 respectively, the radii then would be 5.08 and 2.42. The relative tensions would then be 25.8 and 5.8, and the ratio of differential tensions would now be *4.4:1* instead of *3:1* as before.

Although, therefore, the effect of loss of amniotic fluid through rupture of the membranes is to diminish the absolute tension within the walls of the uterus, the net effect is to increase the tension in the fundus relative to that in the lower uterine segment. If other conditions are satisfied, the delicate balance of forces which is preventing the emptying of the uterus of its contents is tipped suddenly in the direction of their prompt delivery, and the normal pattern of uterine contractions for effective dilatation of the cervix is favored.

SUMMARY

1. Patterns of uterine contractility in women were recorded during the first stage of labor by means of a multichannel tokodynamometer. With this instrument, activity in the fundus, the mid-zone of the uterus, and the lower uterine segment was recorded. The activity was analyzed for the intensity, duration, and work (dynes) of the average contraction at each level. In this way, gradients, and the origin, spread, and dissipation of the wave of contraction could be recorded over the surface of the uterus.

2. Dilatation of the cervix is associated with a gradient of diminishing physiological activity from the fundus to the lower uterine segment. *Deviation from this pattern is associated with prolongation of labor or prevention of dilatation.*

3. The physiological basis of this gradient of activity is discussed with respect to the tissue tensions in fundus and lower uterine segment respectively. It is shown that in the fundus the tension exceeds that in the cervix by about 3:1. This, like the effect of tension in skeletal and cardiac tissues, favors increased

PREGNANCY AND THE THYROID GLAND

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The relation of thyroid activity to sex and its functions has long been recognized, but the particulars of this relationship have been subjects of endless speculation and conflicting hypotheses. Before presenting the few additional facts we have to offer, it may be well to review the facts already available and current opinions on the subject. Women are undoubtedly more susceptible than men to all recognized functional disturbances of the thyroid gland, especially hyperactivity of the organ. The incidence of this latter condition appears to be greater during periods of changing sexual function, adolescence and the menopause. Concerning the effect of pregnancy there is some difference of opinion. It is generally agreed that the thyroid gland undergoes hyperplasia during pregnancy; but there is no certainty that this hyperplasia is attended by hyperfunction. The basal metabolism rises in the latter months of pregnancy (1, 2, 3, 4), but the rate of oxidation is not controlled by the thyroid gland alone. The rise of basal metabolism in pregnancy is not accompanied by other recognized manifestations of hyperthyroidism. Indeed, serum cholesterol is reputed to increase, a phenomenon that is regularly observed in hypothyroidism (5, 6, 7). The hypermetabolism of pregnancy is not regularly accompanied by the circulatory or nervous manifestations that characterize hyperthyroidism.

Clinical hyperthyroidism may begin during pregnancy, but this does not seem to be a frequent occurrence (4). Clinical hyperthyroidism does not appear to influence the normal course of pregnancy nor to prevent conception. Thyroidectomized female animals are unable to conceive. Complete absence of the gland produces sterility in both sexes. This has given rise to the impression that infertility in women with normal menses may be due to some lesser degree of thyroid deficiency. Convincing evidence for such a concept has been hard to find, chiefly because it is impossible, as Means (8) has pointed out, to diagnose with certainty minor or intermediate degrees of thyroid deficiency. It has been claimed by Litzenberg (9) among others that hypometabolism is found with unusual frequency in women who can not conceive and that administration of thyroid to such women may enable them to become pregnant. Hypometabolism, as he defines it, basal metabolism −10 or lower, is not acceptable evidence of hypothyroidism. Javert (4) has suggested that if hypothyroidism were a cause of infertility, hyperthyroidism might be expected to promote fertility. Actually published reports indicate a low incidence of pregnancy among hyperthyroid subjects. He rightly points out that contraceptive practices may contribute to this rate.

Although total removal of the thyroid of the nonpregnant animal produces sterility, once pregnancy has been established, thyroidectomy does not interrupt it (10, 11, 12, 13). Nevertheless, miscarriages, and especially the tendency to

characteristics in the contraction pattern. We have feeble contractions, and a pattern in which no contraction looks like the one preceding or following it. I should be glad if Dr. Reynolds could enlighten us further on these three points.

DR. REYNOLDS: The first question Dr. Murphy asked is, What is the difference between true and false labor? I have already shown records of false labor. I described one instance in which the reason the cervix was not dilating was that the entire uterus, including the lower uterine segment, was contracting, whereas only the upper uterine segment should have been. In another case the duration of the contractions in the mid-zone of the uterus exceeded the duration of those in any other part of the uterus. Consequently, a functional contraction ring developed every time this portion of the uterus contracted.

Dr. Murphy asks why the cervix does not open in prolonged labor. I mentioned the necessary condition for this in my first statement. That is the most significant point we tried to make clear today. When the cervix fails to dilate it is because the activity in the fundus does not exceed that in the rest of the uterus.

With regard to the question concerning uterine inertia, we don't know what happens in all cases. We have been recording TKG's now for 4½–5 months. We have had the usual vicissitudes of getting any program of work started. The number of records we have today is relatively small. I did show records from two cases of uterine inertia, however. What happened in one was that there was an apposition of the breech to cervix with resultant cervical dystocia. In the other case there had been, as far as the record shows, contractility of the entire uterus, including the lower segment, the midsegment and the fundus. As soon as the activity in the lower segment stopped contractions were strong in the fundus, and there was a normal gradient of physiological activity, this patient went ahead and delivered spontaneously in 2 or 3 hours.

pregnancy, it has, as far as can be determined from the data thus far collected, no tendency to deviate in one direction or the other as pregnancy progresses. This is another link in the chain of evidence that the rise of metabolism in the latter part of pregnancy can not be attributed to increased thyroid activity. Bokelman and Scheringer (23) in 1930 reported that the iodine of blood rises early in pregnancy. It is, of course, anomalous that a high concentration of thyroxine in the serum should not be accompanied by hypermetabolism. The question may even be raised whether this precipitable iodine is thyroxine or whether in pregnancy some other iodine compound without calorigenic influence may find its way into the serum. Whether or not this increment of iodine in pregnancy is thyroxine, the precipitable iodine does not rise further in the latter
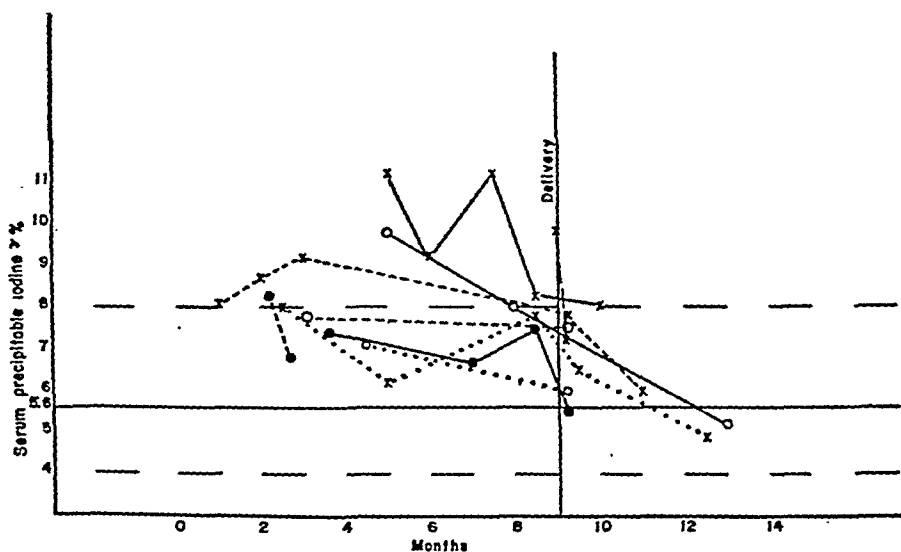
FIG. 1

part of pregnancy as might be expected if the increase of metabolism that characterizes that stage were induced by the thyroid.

Figure 1 shows the course of the serum iodine after pregnancy in a few cases. There is no evidence that the iodine falls before delivery, although the number of observations is too small as yet to warrant certainty on this point. Shortly after delivery it drops to the normal range. How soon this fall occurs is another question that requires further inquiry. From one or two of the observations in the series it would seem to be quite early and quite precipitate.

The crosses on Figure 2 represent patients who had miscarriages, the squares, patients who had bleeding of sufficient severity to warrant a diagnosis of threatened abortion. Eight of the twelve points lie below the concentration of 6.2 γ per cent, the lowest value found among the women with normal pregnancies that went to term. This is not a large number, but the arrangement of points

habitual abortion, have been attributed to hypothyroidism, and thyroid products have been given to prevent abortions (14). Bodansky and Duff (15) claim that pregnancy makes rats more resistant to the effect of thyroid. This may bespeak a greater need for thyroid hormone during pregnancy; it can not be interpreted as evidence of hypothyroidism. Euthyroid subjects can often tolerate larger doses of thyroid than can patients with myxedema. The latter respond to active thyroid substance quantitatively, while animals with thyroid glands appear to be able to inactivate large amounts of such substance (16, 17).

Finally—and here the evidence becomes more and more tenuous—thyroid deficiency has been held responsible for toxemias and other disorders of pregnancy.

With accurate methods for the determination of serum iodine it seemed possible to resolve some of these uncertainties about the relation of thyroid activity to pregnancy and its complications. It has been demonstrated that in functional disorders of the thyroid gland the fraction of iodine which is firmly bound to the proteins of the serum, the precipitable iodine of the serum, reflects with great accuracy the activity of the gland. It appears to be uninfluenced by extraneous factors that affect the basal metabolism, serum cholesterol and other functions that have been generally used as criteria of thyroid activity (16, 17, 18, 19, 20). There is good reason to believe that most or all of the precipitable iodine of serum actually consists of thyroxine or active thyroid hormone. Thyroxine, when added to serum *in vitro*, attaches itself firmly to the proteins, behaving like the inherent precipitable iodine (21). Recently Taurog and Chaikoff (22), by the technique of isotope dilution, using thyroxine labelled with radioactive iodine, have more directly identified the precipitable iodine of normal serum with thyroxine. The present report deals chiefly with the concentrations of precipitable iodine in the sera of pregnant women, measured by the method of Man, Smirnow, Gildea and Peters (21).

RESULTS

In Figure 1 the circles indicate the concentrations of precipitable iodine in the sera of women with normal pregnancies that went to term. There are altogether 38 observations on 22 women from the second month to the day of delivery. The horizontal lines represent the limits of variation of precipitable iodine in normal, nonpregnant women, 4 to 8 γ per cent. The precipitable iodine of the pregnant woman is distinctly higher, ranging from 6.2 to 11.2 γ per cent. In fact, the average value, 8.3 γ per cent, is just above the maximum nonpregnant value. Further figures confirming these have been obtained, but are not shown on the figure because the women from whom the sera were obtained have not yet come to term. None of these women presented symptoms or signs of hypothyroidism. The elevation of iodine does not follow the course of the basal metabolism. The latter rises gradually after about the fourth month of pregnancy (3, 4) whereas the precipitable iodine is already high as early as it is possible to make a diagnosis of pregnancy, as soon as the Aschheim-Zondek test is positive. Furthermore, although it may fluctuate somewhat in the course of

thyroid. In contrast to the patients in the first figure, the pregnancies of the women in this series proceeded without interruption, most of them to delivery (the remainder have not yet reached term). That such success can not be predicted consistently will be pointed out in the discussion of one or two exceptional cases later. It will be noted that in 4 instances the precipitable iodine did not rise above 6 γ per cent within the first 4 months of pregnancy. In every case, however, it did rise under the influence of thyroid therapy, approaching 6 γ per cent. The intervals between points are so long that the lines connecting them do not represent the course of the iodine, but only serve to identify the values with the individual patients. Presumably the iodine in every case rose more rapidly.
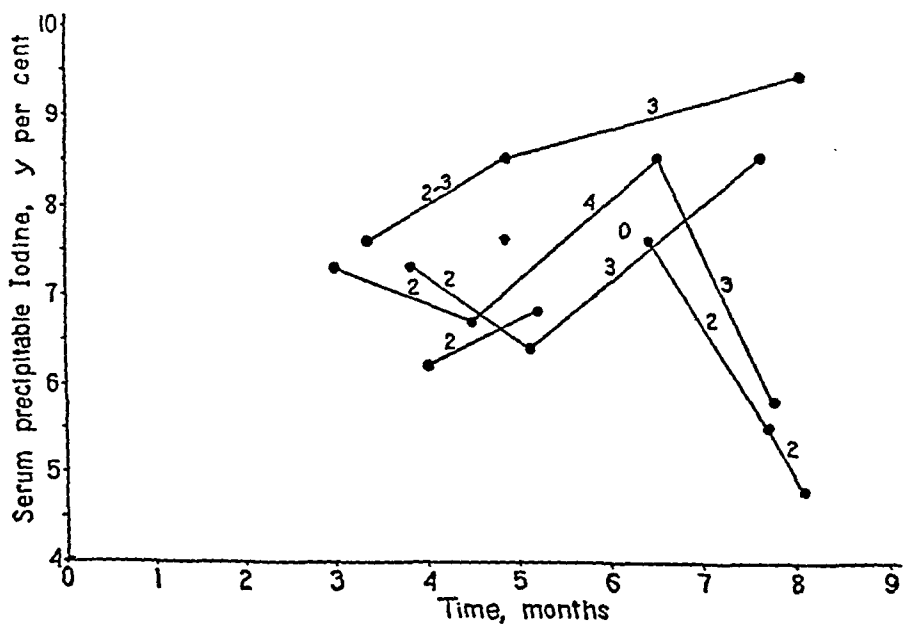
FIG. 3

In only one woman did it rise above 8 γ per cent, although 2 received as much as 4 grains a day for considerable periods. This does not signify that these pregnant women had an exceptional tolerance to thyroid.

In Figure 4 are shown a group of patients with serum iodines initially above 6 γ per cent who were, nevertheless, for various rather dubious reasons, given from 2 to 4 grains of thyroid daily. All were free from stigmata of thyroid dysfunction. The responses do not differ essentially from those elicited in patients with low initial serum iodine. In the second group, since iodine was higher in the beginning, it rose above 8 γ per cent more frequently. In both series, after prolonged administration of thyroid, precipitable iodine sometimes fell while medication continued. This again must not be interpreted as unusually high tolerance to thyroid because many apparently normal persons respond in the

on the figure could hardly be accidental. The reason the number is not larger is an illustration of the human factors with which clinical research has to contend. As soon as it seemed even possible that a low serum iodine might portend miscarriage, those responsible for the medical care of these women could not refrain from administering thyroid. The direct line of investigation can, therefore, progress only as material is accidentally obtained. The data on this figure alone suggest that if the precipitable iodine of the serum is low early in pregnancy a
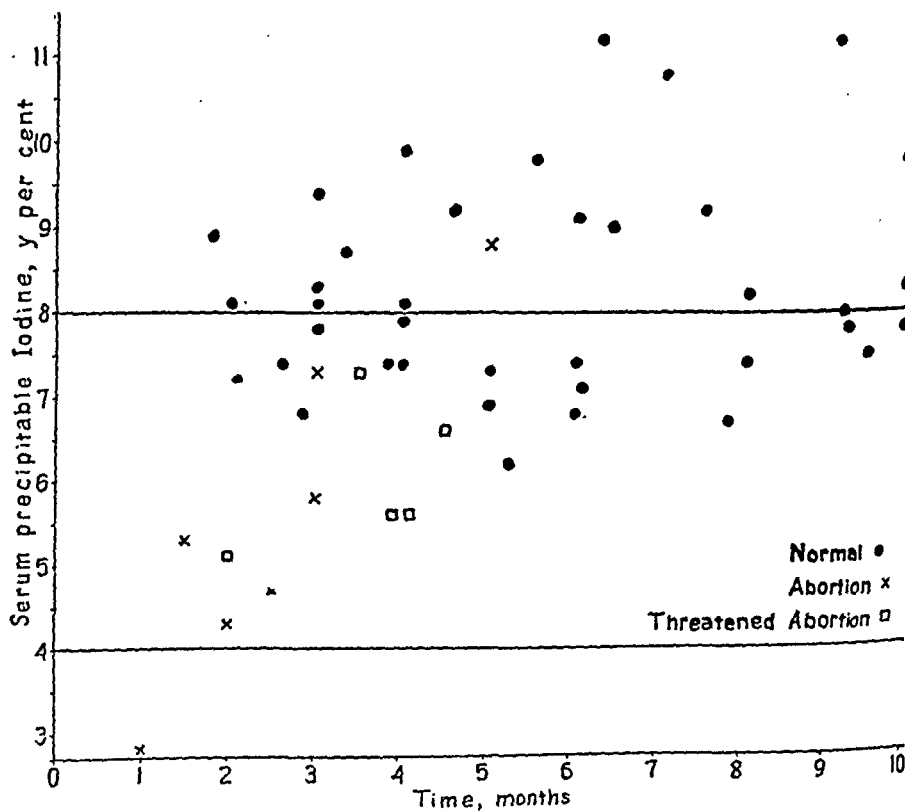
FIG. 2

miscarriage will probably occur. This impression is supported by the absence of low points after the fourth month. On the other hand, the presence of crosses and squares at iodine concentrations greater than 6 γ per cent means that low serum iodine is not the only cause of miscarriage. It remains to add that, just as the high iodines of normal pregnancy are not accompanied by symptoms or signs of hyperthyroidism, so the women with low iodines who aborted had no stigmata of hypothyroidism.

Certain inferential evidence has been gained in other ways. In Figure 3 is shown the course of the precipitable iodine of 7 patients who, having been discovered to have serum iodines below 6 γ per cent, were given various quantities of

per cent. It is impossible from the concentrations of iodine in the serum of a nonpregnant woman to predict with any certainty her reaction during pregnancy. From the first 3 cases for which both pregnancy and interpregnancy figures are given it may be seen that patients with relatively low iodine values in the interpregnant state have higher than normal values during pregnancy. In the group that had miscarriages the iodines rose but little during pregnancy when they did rise, and in some cases fell. This brings out the fact that failure of the iodine to rise in the normal manner during pregnancy does not bespeak an antecedent thyroid deficiency so far as this can be judged from serum iodine, but rather an

TABLE 1

Patients with histories of miscarriages

NAME	SERUM PRECIPITABLE I		MONTH	REMARKS
	Not pregnant	Pregnant		
	γ per cent	γ per cent		
Po	4.1	2.8	0.75	2 miscarriages
Sp	5.0	3.9	2	2 miscarriages, 2 children
Mi		4.1	1.5	2 miscarriages, 2 children
Hor	5.6	4.6	1.5	2 miscarriages
Gi	5.5	4.8	1.5	On 1 gr. thyroid
Hi	3.8	5.1	1.5	2 previous miscarriages
Le	4.5	5.3	1.5	1 miscarriage
Is		5.4		1 miscarriage
Be	3.5	5.8	3	1 miscarriage
Parm		5.8	3	2 premature deliveries
Pars	5.1	6.3	2	2 miscarriages
Bu		7.2	2.5	4 miscarriages
Zu		9.4	4.5	2 miscarriages, at 6 and 3.5 mos. This pregnancy has proceeded 9 mos.
Hol	5.5			2 miscarriages, 2 children
Jo	4.7			1 premature delivery at 6 mos.
Lyn	6.1			2 miscarriages
Lyo	5.5			2 miscarriages, 1 child
Na	5.8			2 miscarriages
Sh	5.1			Several miscarriages

improper reaction to the state of pregnancy. It is, of course, possible, indeed probable, that patients with deficient thyroid activity would have low serum iodine during pregnancy and a tendency to miscarriage.

In Table 3 are the serum iodines of women who sought advice because they were unable to become pregnant. Serum iodine was within normal limits in all. A surprisingly high normal value was found in one who had not menstruated for 8 years, while one of the lowest values came from one whose fertility had been proved, although she had not been successful in expanding her family to the desired extent. This lends little support to the opinion that thyroid deficiency is a frequent cause of infertility, despite the fact that myxedema causes sterility.

same manner. It may be noteworthy that when the iodine fell below 6 γ per cent in late pregnancy, the pregnancy was not interrupted. This suggests that in the more advanced stages low serum iodine is no obstacle to pregnancy. This should follow from the fact that in animals after pregnancy is well established thyroidectomy does not interfere with its progress. Chu (13) found that thyroidectomy in the rabbit at an early stage of pregnancy caused resorption and abortion of the embryos, while at a later stage of pregnancy it resulted in the delivery of stillborn young. Apparently the latter is not true in other species. Chu's experiments do however indicate that the reaction to absence of thyroid
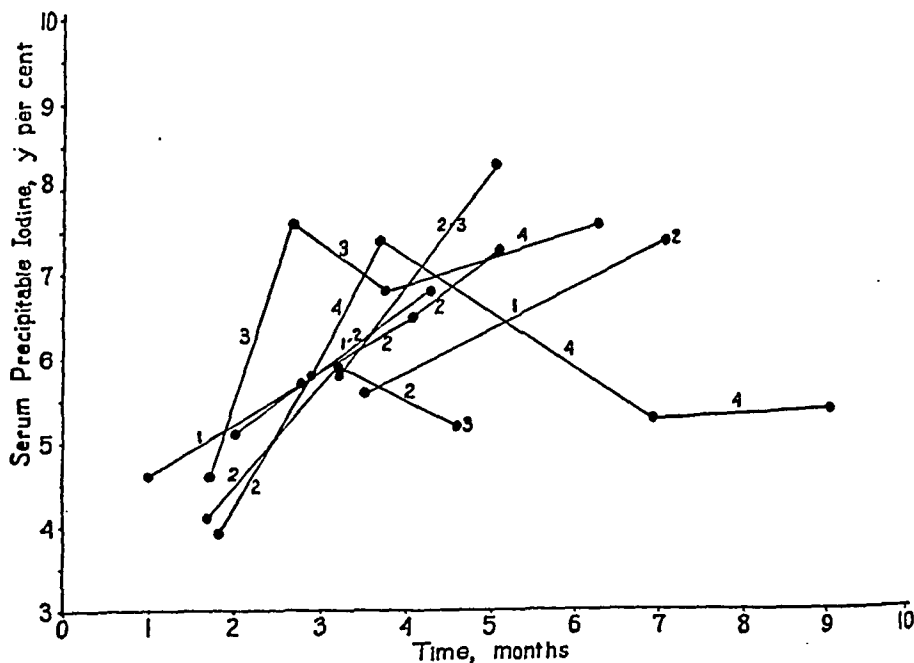
FIG. 4

differs as pregnancy progresses. The reaction in the early stages of pregnancy is like that which Chu noted when he succeeded in impregnating thyroidectomized rabbits.

In Table 1 are shown the concentrations of iodine in the sera of patients who have had miscarriages, taken in the intervals between pregnancies and, in some cases, during pregnancies. In 10 cases the values during pregnancy were less than 6 γ per cent. On the other hand, only 2 out of 14, when not pregnant, had values lower than 4 γ per cent. In Table 2 are shown in the same manner the concentrations of iodine in the sera of patients who have had pregnancies without miscarriages. A few figures are higher than those from the group that had miscarriages, but the averages in the two tables differ by only 0.7 γ per cent. In one instance in the series without miscarriages the serum iodine was only 3.9 γ

This must be considered as only a preliminary report and most of the deductions must be regarded as tentative hypotheses. The data are too incomplete to warrant definite conclusions. It does seem clear that for some reason the precipitable iodine of the serum rises during normal pregnancy. The evidence to date suggests also that if the serum iodine does not rise abortion is likely to occur in the early months of pregnancy. What relation the high serum iodine may have to activity of the thyroid gland is another question. It is possible that the increment in pregnancy is not, like the normal precipitable iodine, composed of thyroid hormone. Neither the patients with high nor those with low iodine have recognizable symptoms or signs of thyroid dysfunction. Serum lipids, which have been measured in a few cases, can not be correlated with iodine. This aspect of the subject is now under investigation. The best evidence that the precipitable iodine in pregnancy is thyroxine would be the demonstration that low serum iodine did interfere with the progress of pregnancy and that the administration of active thyroid substance both raised the serum iodine and prevented early abortion. Substantial, but not conclusive, evidence to this effect has been obtained. Three cases deserve especial description in this connection.

Gi (see Figure 5) had for some years, without good evidence of hypothyroidism, taken thyroid. During this period she had 2 normal pregnancies. After this she stopped taking thyroid. During this period she had three miscarriages. On June 29, 1945, while she was not pregnant and receiving no thyroid her serum precipitable iodine was 5.5 γ per cent, a normal figure. Her basal metabolism was −16 per cent, but she had no symptoms nor signs of hypothyroidism, although she had not menstruated for a year. August 24 she was started on 1 grain of thyroid per day. September 15 she menstruated, but skipped her next period. November 1 the serum precipitable iodine was 4.8 and November 30 it was only 5.1 γ per cent. Pregnancy was suspected, but the Aschheim-Zondek test on December 11 was reported negative. The dose of thyroid was, nevertheless, increased to 1.5 grs. daily. February 3, 1946, when the serum iodine was 6.6 γ per cent, she began to have labor pains and bleeding. These stopped promptly after the intravenous administration of 2 mg. of thyroxine which was repeated on the following day. On February 6 the serum iodine was 18.8 γ per cent. She was given at this time 2 grs. of thyroid daily, which was increased to 3 and then to 4 grs. as the effect of the thyroxine wore off. She had a normal delivery on August 5.

Po did not menstruate until 15, and then for a time had scanty periods. For this reason, because she complained of lack of energy and because her basal metabolism was reported to be −44 per cent, she was given thyroid in gradually increasing doses up to 5 grs. daily, which she took until November 2, 1946. This had never caused symptoms of hyperthyroidism. At the time she stopped she was 3 months pregnant. The next day, November 3, she had a miscarriage. There is no intention of stressing this coincidence. On December 5, 5 weeks

In Table 4 are 4 cases of toxemia serious enough to require termination of pregnancy, together with 2 cases of pyelitis in pregnancy. All had the higher serum iodines characteristic of normal pregnancy. The number of cases is too small to warrant any conclusions. It is, however, hard to conceive that toxemias,

TABLE 2

Patients 8 histories of miscarriages

NAME	SERUM PRECIPITABLE I		MONTH
	Not pregnant	Pregnant	
	γ per cent	γ per cent	
Mc........	6.0	8.1	1.5
Eu........	5.2	9.8	5.5
Sh........	4.9	8.1	3.0

NOT PREGNANT			
Name	γ per cent	Name	γ per cent
DI.........	6.2	Le.......	6.3
Fi.........	6.1	Ma......	5.6
Bu.........	4.3	Ne......	4.7
Ga.........	5.1	Qu......	5.8
Hel........	6.9	Re......	3.9
Hu.........	4.3	Sm......	5.7
Hes........	5.2	Te......	5.0
Joh........	7.8	Th......	6.8
Jos........	7.5	Val......	6.4
Pu.........	5.7	Van.....	5.7
Kr.........	5.0	Pr.......	4.1

TABLE 3

Infertility

SERUM PRECIPITABLE I		REMARKS
γ per cent	γ per cent	
5.7	5.7	
5.9	6.8	
5.5	5.4	
5.1	7.2	
4.6	4.8	
5.0	6.0	
5.3	6.4	
5.1	6.2	
4.2	7.9	Amenorrhea 8 years
6.1	4.2	On thyroid gr. 1
		2 previous children

TABLE 4

Toxemias of pregnancy

NAME	MONTH	SERUM I	REMARKS
		γ per cent	
No......................	7	8.4	Terminated 2 days later
Fo......................	2.5	8.3	Terminated 6 weeks later
He......................	2	6.9	Previous toxemia. Terminated
Ro......................	2	7.0	Previous toxemia. Terminated
Jos......................	8	7.8	Puelitis. Went to term
Joh......................	6	8.2	Pyelitis. Went to term

which are a manifestation of late pregnancy, could with any frequency be accompanied by low serum iodine if the latter leads to miscarriage in early pregnancy. If such a combination did occur, the natural inference would have to be, not that hypothyroidism provoked toxemia, but that toxemia caused serum iodine to fall.

Granted that the increment of precipitable iodine in the serum during preg-
nancy is thyroid hormone, its significance is still enigmatical. What purpose
does it serve? It apparently does not exert its usual action of accelerating
metabolism. It does not rise progressively, as if it were utilized for the processes
of new growth connected with pregnancy; but precipitately, as if it were con-
cerned rather with the fundamental transformation that is pregnancy. That
the pregnant woman is susceptible to the calorigenic effect of thyroid hormone is
attested by the records of patients who have had spontaneous hyperthyroidism
during pregnancy. It is worth remarking that subtotal thyroidectomy in this
condition need not precipitate abortion. The present data indicate that the
pregnant woman can tolerate considerable doses of thyroid without excessive

TABLE 5

Po, Born 1922. Married in 1945

1946
  Nov. 2—Stopped taking 5 grs. thyroid daily, 3 months pregnant.
  Nov. 3—Miscarriage.
  Dec. 5—Serum precipitable iodine 4.1 γ per cent.
  Dec. 11—Apparently normal menstrual period.
  Dec. 30—Serum precipitable iodine 2.8 γ per cent.

1947
  Jan. 2—Miscarriage.
  Jan. 22—Serum precipitable iodine 4.4 γ per cent.
  Jan. 24—2 grs. thyroid daily.
  March—Missed period.
  Apr. 7—4 grs. thyroid daily.
  Apr. 14—5 grs. thyroid daily.
  Apr. 23—Serum precipitable iodine 8.3 γ per cent.
  June 3—Serum precipitable iodine 10.0 γ per cent.
  Sep. 15—Serum precipitable iodine 8.6 γ per cent.
  Nov. 15—Spontaneous delivery.

rise of serum iodine or the appearance of toxic symptoms; but in this she does
not differ demonstrably from a large proportion of her nonpregnant sisters. No
one of the pregnant women in this series failed to react to doses of 2 to 4 grs. of
thyroid; but Le, took 5 grs. without any effect on her serum iodine after she had
aborted. The pregnant woman resembles the nonpregnant in developing a
tolerance for exogenous thyroid substance and a greater ability to dispose of it
when it is given in large doses. This was pointed out in the discussion of the
two instances in which serum iodine fell, after a preliminary rise, to low figures
in two subjects who were taking respectively 3 and 4 grains of dried thyroid
daily.
    It has been claimed that pregnant women require and excrete unusually large
quantities of iodine (24). Hertz and associates (25) have shown that the thyroid
glands of rabbits take up radioactive iodine with unusual avidity. Both these
observations indicate that the turnover of thyroid hormone is more rapid in

after discontinuing thyroid, the serum precipitable iodine was 4.1 γ per cent. On December 11 she had what appeared to be a normal menstrual period. On December 30 the serum iodine was only 2.8 γ per cent. January 2, 1947, she started to bleed and discharged material that proved histologically to be the product of another abortion. January 22 the serum iodine was 4.4 γ per cent. Two days later, on January 24, she was started on 2 grs. of thyroid daily. At this time she moved from New Haven to Cleveland. In March she missed a period. On April 7 her thyroid dose was raised to 4 grs. and on April 14 to 5 grs. daily. Subsequent serum iodines were: April 23, 8 γ per cent; June 3, 10
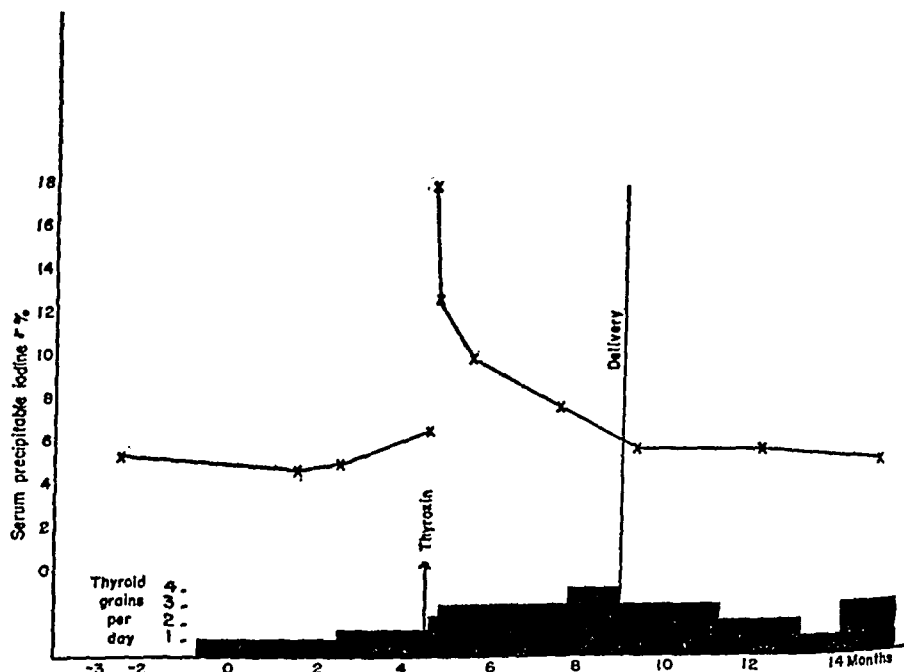
FIG. 5

γ per cent; September 15, 8.6 γ per cent. November 15 she delivered spontaneously at term a normal girl (Table 5).

Le had also taken thyroid for a time without definite evidences of hypothyroidism. Early in the summer of 1947 she had a miscarriage during her first pregnancy. October 20, while she was presumably not pregnant and was receiving no thyroid, her serum precipitable iodine was 4.5 γ per cent. November 24, after having skipped a period, she began to bleed. Her precipitable iodine at this time was 5.3 γ per cent. She was immediately started on 5 grs. of thyroid daily. The bleeding stopped. On December 20, in spite of this large dose, the iodine had dropped to 4.8 γ per cent. The next day she delivered material that evidently indicated that the episode of November 24 had been not a threatened, but a missed abortion.

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DISCUSSION

DR. WILLIAM C. YOUNG: At the University of Kansas we have been working on the relationship between the level of thyroid activity and reproductive performance. Although we have not yet perfected Dr. Salter's technique for the determination of precipitable iodine in serum, we are producing hypothyroid guinea pigs by means of the administration of 6-propyl thiouracil, and a study of the thyroids has convinced us that their hyperplastic condition, which is clearly evident at the end of 60 days' treatment, is evidence for the hypothyroid state. We have obtained some results which are fairly definite. They indicate that hypothyroidism in the guinea pig does not have the serious effect on the course of gestation that it does in other laboratory mammals and man.

I have here the data from approximately a dozen pregnancies. In each case the female was impregnated between 70 and 120 days following the beginning of thiouracil administration. In only one case was there a termination of pregnancy as early as the 35th day. The gestation period in the guinea pig is 68 days. In several of our cases there was a stillbirth between the 60th and 65th day, which is fairly common in the guinea pig, and in at least 5 cases there was normal delivery between the 68th and the 70th day. It has been interesting to us that in all the abortuses recovered between the 63rd and 65th day, and in all animals born alive between the 68th and 70th day, the fetal thyroids were tremendously hyperplastic. We have not enough measurements from the thyroid of the newborn guinea pig to state what the extent of the hyperplasia is, but I would estimate that the experimental thyroids are 100 times heavier than those in newborn animals born to untreated parents.

pregnancy. If this were due merely to more rapid destruction or excretion of thyroxine, it should not manifest itself chiefly in increased serum iodine. Besides the effects of thyroid administration do not indicate any increase in these processes alone. Nor do they reveal any striking difference in the reaction of the persons with high and with low iodines to exogenous thyroid. The latter do, however, appear to require greater amounts of iodine.

CONCLUSIONS

The precipitable iodine of the serum rises sharply at the onset of pregnancy from the normal concentration of 4 to 8 γ per cent to concentrations between 6 and 10 γ per cent, and remains at these levels until delivery, after which it rapidly returns to the normal range. This rise is not accompanied by other manifestations of increased activity of the thyroid gland. There is reason to identify the increment of iodine with the thyroid hormone.

There is evidence to suggest that failure of the precipitable iodine to rise at the onset of pregnancy leads to early miscarriage which may be prevented by the administration of active thyroid substance. Low precipitable iodine in these cases is not accompanied by other manifestations of thyroid deficiency.

The serum precipitable iodine in pregnancy does not appear to be consistently related to the concentration of iodine preceding pregnancy.

No evidence has been found in a limited number of observations that serum precipitable iodine is abnormal in women with infertility or suffering from toxemias of pregnancy.

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EXCRETION OF VARIOUS HORMONE METABOLITES
IN NORMAL PREGNANCY

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The intimate role that the endocrine glands play in the development and maintenance of pregnancy needs no emphasis. Chiefly responsible for the advances made in this field has been the development of relatively simple methods for the assay of the various substances elaborated by these glands. Through the use of these methods ovarian and placental hormones have been isolated and characterized and their functions established. The application of these assays to the study of the excretion of hormones and their metabolites in man has revealed the physiologic relationship existing between the various glands during the menstrual cycle and throughout pregnancy. The 3 hormones principally concerned in reproduction are, the gonadotropins, the estrogens, and the corpus luteum hormone, progesterone.

Through a period of approximately 10 years, in collaboration with Dr. J. S. L. Browne and others, studies on the excretion rates of these substances have been made in pregnancy and non-pregnancy under a variety of conditions.

METHODS

The urinary gonadotropins have been assayed upon the immature female rat, the production of a full squamous response in the vaginal smear of this test animal being taken as a positive end point. For the urinary estrogens, two methods have been used, (a) a bioassay method for the determination of these substances in the menstrual cycle, where the values are low, and (b) the colorimetric method of Venning et al. (1) for their determination in pregnancy.

The corpus luteum hormone, progesterone, is not excreted as such but is metabolized in the body into pregnanediol and pregnanolone and is excreted as glycuronides of these substances. The precipitate obtained by the method of Venning (2) has been shown by Marrian and Gough (3) to contain at least two glycuronides which are determined together. This mixture is referred to as the pregnanediol complex. Metabolic studies carried out by Venning and Ripstein (4) have shown that in man both pregnanediol and pregnanolone are excreted in urine following the administration of crystalline progesterone. These two substances, therefore, should be considered together when evaluating progesterone metabolism.

This work represents only a beginning, but it indicates that if there is any effect of hypo-thyroidism in the guinea pig, the effect is shown late rather than early in the gestation period, and is not incompatible with the normal termination of pregnancy.

CHAIRMAN HERTIG: Thank you, Dr. Young. Dr. Peters, do you care to respond?

DR. PETERS: Of course we carefully avoided the discussion of hypothyroidism, because we don't know the relation of these phenomena to this condition.

There is certainly a differentiation among species which is brought out by the experiments of Hertz which I cited. The dog can not be impregnated if it is myxedematous or has no thyroid, but can carry on well if the thyroid is removed after impregnation. That is the way goitrous puppies were developed. On the other hand, the rabbit can apparently be impregnated with difficulty after the thyroid has been removed. These species differences extend into all features of thyroid function. The dog is a poor animal for studies of iodine because it normally has a serum iodine of only 2 gamma per cent. With available methods it is difficult to evaluate changes at such a low concentration. The dog responds rather weakly to removal of the thyroid. It runs around, plays and eats in a pretty normal way. At the same time its pregnancy rhythm appears to be more disturbed than that of the rabbit.

The discussion of hyperplasia in this connection is a little bit out of line with the phenomena of pregnancy. This hyperplasia is associated with diminution of function in a big way. The hyperplasia that occurs in thyroid disease and the one which occurs in pregnancy are not necessarily related. The glands in these two conditions take up, according to Hertz, far more iodine that the normal gland does, unlike the thiourea gland which takes up less than normal.

DR. CHARLES MAZER: The question is, Dr. Peters, what is the relative efficiency of your test as compared with the basal metabolism in the cases you have cited?

DR. PETERS: In the first place, as I said, the two tests do not follow the same course in all conditions. I think the basal metabolism must be discounted. It is a measure of thyroid function only under certain conditions. There are all kinds of calorigenic agents other than the thyroid. Besides that, in pregnancy there is no increase of basal metabolism associated with the rise of serum iodine, no diminution in those patients in which it fails to rise. That is, there is no increase at the time the rise occurs. The high iodine appears as early as the Aschheim-Zondek test. The basal metabolism in normal pregnancy does not begin to rise until the fourth month, when it goes up slowly. The increase of basal metabolism in normal pregnancy is demonstrable statistically rather than individually. It attains an average maximum of about plus 16 per cent at the end of pregnancy. The iodine values, on the other hand, are of the magnitude that would ordinarily be associated with hyperthyroidism. With some as high as 11 γ per cent a basal metabolism of plus 40 per cent might be expected.

luteum causing it to continue to secrete progesterone and estrogens, thus promoting the formation of decidua in the uterus. In this respect it has been shown that the luteal phase of the menstrual cycle can be prolonged by the administration of adequate amounts of chorionic gonadotropins. However, a continuation of the dose of chorionic gonadotropins at the same level fails to maintain the corpus luteum indefinitely, and pregnanediol excretion decreases and bleeding occurs in spite of continued injections. These facts suggest that the corpus luteum of pregnancy requires increasingly larger amounts of gonadotropins to maintain its function as it grows older and that the rapidly rising output of chorionic gonadotropin in early pregnancy is necessary for this purpose.

In Fig. 2 is shown the urinary excretion of gonadotropins throughout pregnancy. In early pregnancy the gonadotropins increase at a rapid rate reaching a maximum about 50–70 days after the beginning of the last actually occurring menstrual period (6). The height of this peak varies considerably in different cases ranging from 40,000–200,000 rat units per 24-hours. If assays are carried out on first morning specimens, values as high as 300,000 rat units per liter have been found. These very high concentrations are in the order of those found occurring in cases of chorionepithelioma; however, in normal pregnancy the maximum excretion is maintained for only a short time and is followed by a rapid decrease in excretion rate. By approximately the 110–120th day the level of urinary gonadotropins is between 5000 and 10,000 rat units per 24-hours. In most cases of normal pregnancy, from this time on until parturition the urinary gonadotropins remain relatively constant varying between 1000 and 10,000 rat units per 24-hours. In a few normal cases, however, a secondary rise in gonadotropins has been observed in the last trimester, lasting for varying periods of time. A late rise in both urinary and serum gonadotropins has been shown to occur in cases of toxemia of pregnancy. No significant changes occur in the rate of excretion of gonadotropins just prior to delivery. Following parturition, the gonadotropins decrease to a low level in the urine within 3 to 10 days.

Transport of ovum

The excretion of hormones in early pregnancy has also shed some light on the time taken by the ovum to be transported down the tubes and become embedded in the uterine mucosa. From our studies in the menstrual cycle ovulation occurs just after the rise in excretion of gonadotropins at the midcycle, and just prior to the appearance of pregnanediol in the urine. The time of implantation of the fertilized ovum coincides with the reappearance of urinary gonadotropins in the late luteal phase. The interval of time between ovulation and implantation in 3 cases studied has been in the order of 9, 10, and 12 days respectively.

With implantation of the fertilized ovum, the corpus luteum is maintained by the increasing amounts of chorionic gonadotropins elaborated by the growing trophoblast. There is a continuation in the excretion of pregnanediol either at levels found in the menstrual cycle or at slightly higher levels. Estrogens increase somewhat over the level found in the menstrual cycle. The time at which the rate of excretion of these substances begins to rise varies considerably

EXCRETION OF HORMONES IN THE MENSTRUAL CYCLE

The hormonal relationships existing between the estrogens, progesterone, and gonadotropins in the menstrual cycle are illustrated in Fig. 1. Gonadotropins are present only in negligible amounts during the entire menstrual cycle with the exception of the time of ovulation. Occasionally peaks of excretion are seen during the menstrual bleeding or just prior to it, but as yet no significance has been attached to these. Estrogens increase from a very low level after the menses to a peak at about ovulation time. This is followed by a slight decline and subsequently by a second premenstrual rise. The excretion of estrogens is low just before and during the menses. Urinary pregnanediol is absent during the follicular phase of the menstrual cycle, rises gradually after ovulation to a peak about the middle of the luteal phase, and then falls to very low levels just prior to the onset of bleeding. In normal women the interval of time between
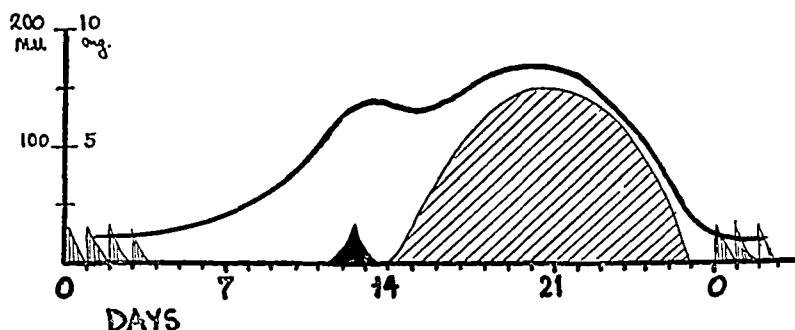
FIG. 1. EXCRETION OF GONADOTROPINS, ESTROGENS AND PREGNANEDIOL
COMPLEX IN THE MENSTRUAL CYCLE

the appearance of pregnanediol and the occurrence of the next menstrual bleeding is fairly constant regardless of the length of the menstrual cycle, usually ranging from 11 to 14 days. At the peak of the luteal phase pregnanediol excretion is in the order of 5–10 mg. per 24 hours. A total excretion of 30–60 mg. is generally considered as normal. Menstruation occurs within 1 to 3 days following the disappearance of pregnanediol from the urine. Estrogen excretion also decreases prior to the onset of bleeding. The sudden withdrawal of both estrogens and progesterone is responsible for the changes that result in breakdown of the uterine endometrium and subsequent bleeding.

EXCRETION OF HORMONES IN PREGNANCY

Gonadotropins

Early pregnancy may be considered as a continuation of the menstrual cycle. If the ovum is fertilized and implantation occurs, then gonadotropins appear almost immediately in the urine and within a few days the excretion of these substances increases rapidly. This chorionic gonadotropin is produced by the cells of the trophoblast and has as its function the stimulation of the corpus

as pregnanediol contains appreciable quantities of pregnan-3α ol-20-one.   Both these substances are metabolites of progesteronè and in all the studies reported so far they have been included together and reported as pregnanediol.

A large series of observations on pregnanediol excretion rates determined on pregnancies which were considered normal from a clinical standpoint have been charted in Fig. 3.   During the first 120 days, the values fall within a narrow range but with advancing pregnancy greater variations are observed.   In a large

FIG. 3. EXCRETION OF PREGNANEDIOL COMPLEX IN PREGNANCY

number of cases a maximum excretion is reached around the 220th to 240th day. The excretion rate may either remain at this level or may decrease somewhat before delivery but no marked fall in the output has been observed just prior to the onset of labor.   At term most values fall between 50 and 100 mg. per 24-hours.   In a very few cases amounts as high as 150 mg. per 24-hours have been recorded.   It has also been observed in several cases of normal pregnancy that the excretion rate may increase steadily up to term.   As it will be seen later in individual cases, in both the pregnanediol and estrogens, the increase in output is not a gradual one; there is considerable fluctuation in the same patient.   Following delivery and separation of the placenta, the pregnanediol disappears rapidly from the urine.

·in presumably normal cases, but in most cases an increase is observed between the 60th to 80th day after the last menstrual period.
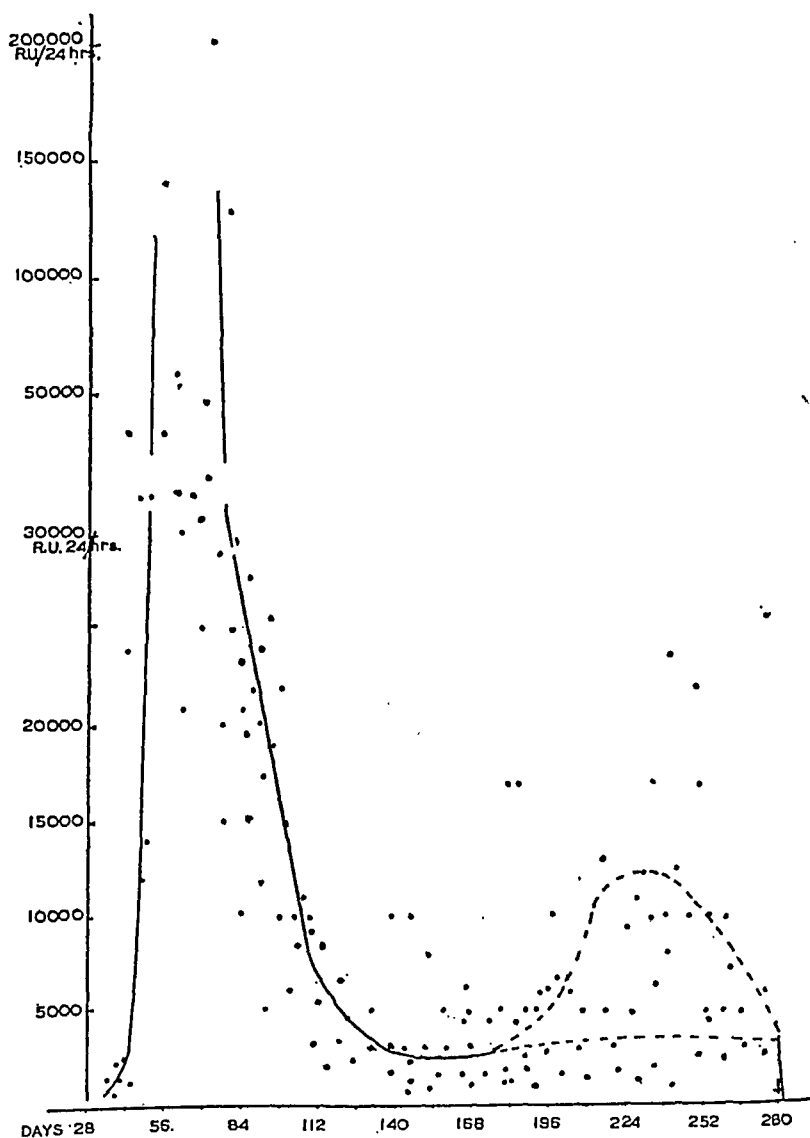
FIG. 2. EXCRETION OF CHORIONIC GONADOTROPINS IN PREGNANCY

Pregnanediol Complex

In the reduction of progesterone to pregnanediol various intermediate metabolites may be formed and several of these have already been isolated from pregnancy urine. It is now known that the mixture which had been measured

as pregnanediol contains appreciable quantities of pregnan-3α ol-20-one. Both these substances are metabolites of progesterone and in all the studies reported so far they have been included together and reported as pregnanediol.

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Estrogens

In pregnancy the excretion curve of the estrogens follows a similar pattern as that of pregnanediol as shown in Fig. 4. In this chart, the total estrogens have been determined by a colorimetric procedure and are expressed in terms of micrograms excreted per 24-hours. Estrogen excretion is low in early pregnancy and does not appear to increase significantly until the 100th day after which time it rises rapidly and may in some cases reach values from 40,000–50,000 γ per 24-hours. Unlike pregnanediol excretion, which plateaus off around the 230th day, the estrogens continue to rise up to the time of delivery, and in many cases there is a rapid increase in the last few weeks of gestation.

Removal of Corpus Luteum of Pregnancy

Although the corpus luteum is undoubtedly necessary for the maintenance of early pregnancy, it has been known for many years that in man it can be removed at a relatively early time without disturbing the course of pregnancy. The continued excretion of pregnanediol and estrogens in cases where the corpus luteum of pregnancy has been removed together with the fact that with the removal of the placenta the excretion of these hormones rapidly decreases, supports the view that the placenta takes over the function of the corpus luteum in the maintenance of pregnancy. Studies have been carried out on two patients in whom pregnancy continued to term following removal of the corpus luteum of pregnancy:

The first patient was in her third month of pregnancy. The right ovary, which contained a small cyst whose pedicle had become twisted causing a hemorrhage into the remainder of the ovary, was removed on approximately the 98th day. On section it proved to contain the corpus luteum. The left ovary was very small and contained no sign of luteal tissue. Pregnanediol continued to be excreted at a normal rate up to the time of delivery. The estrogen excretion rose throughout pregnancy but remained at somewhat lower than normal levels until the last week.

The second patient, case C—Fig. 5, was in her second month of pregnancy. Because of an ovarian cyst, the right ovary, containing the corpus luteum of pregnancy, was removed on the 54th day. Following this, 5 mg. of progesterone were administered daily for 6 days. The pregnanediol output was 3 mg. per 24-hours on the 56th day. Ten days later the level had increased to 8 mg. per 24-hours. Pregnanediol continued to be excreted up to term but values remained below the normal range. The estrogens, on the other hand, were within normal limits. The gonadotropins were apparently not influenced by the removal of the corpus luteum for on the 58th day they were 170,000 rat units per 24-hours and thereafter decreased at a normal rate.

These cases demonstrate that at an early date the placenta is capable of producing adequate amounts of progesterone and estrogens for the maintenance of pregnancy. That the fetus is not concerned with the elaboration of these hormones was observed in a case where the fetus was destroyed from below and a
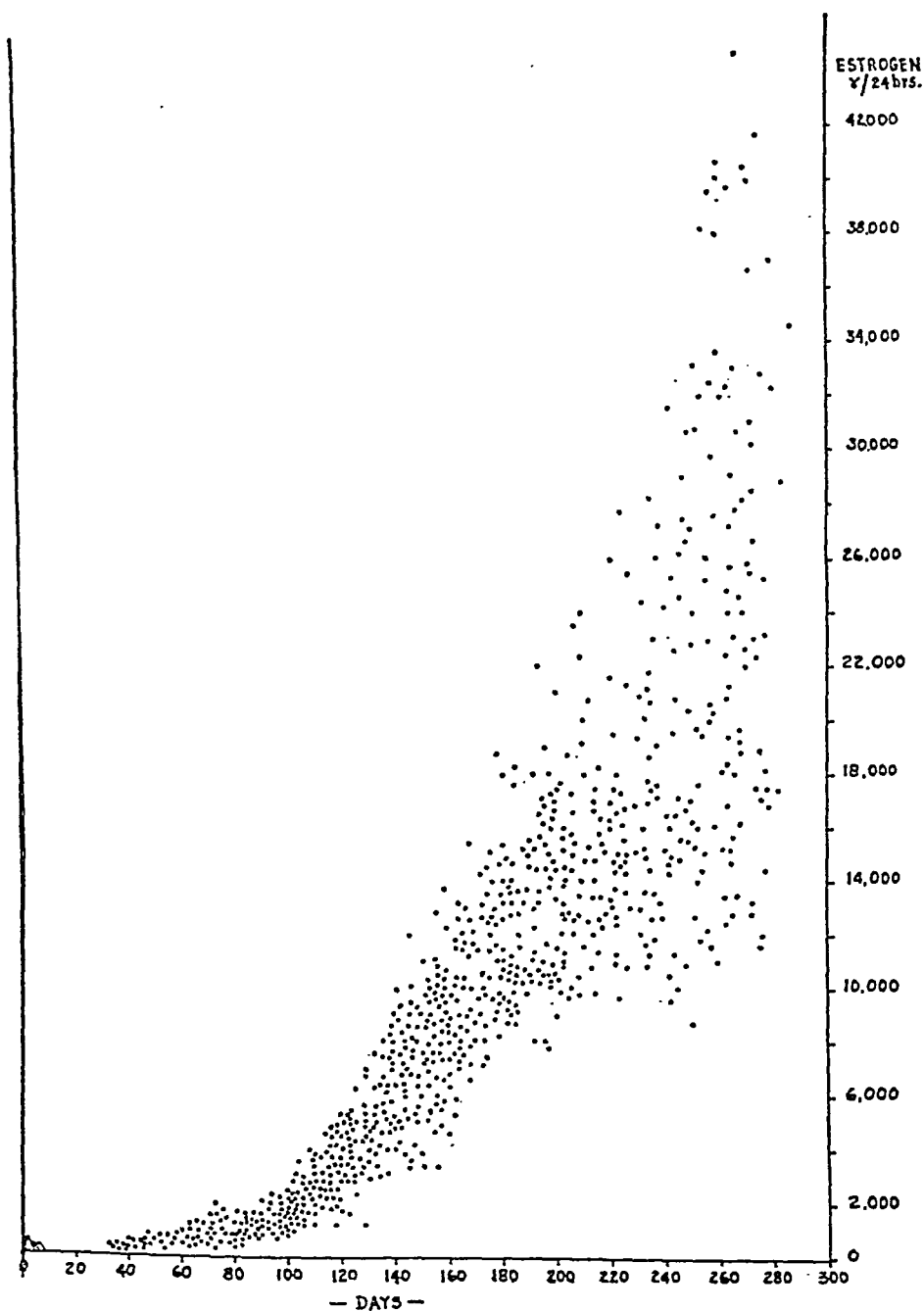
FIG. 4. EXCRETION OF ESTROGENS IN PREGNANCY

normal placenta remained attached for several days, pregnanediol continued to be excreted in normal amounts for the time of gestation.

The transfer of site of formation of estrogens and progesterone from ovary to placenta is probably a gradual one being completed between the second and third month. The time at which the early rise in excretion of pregnanediol takes place is an indication of the increasing activity of the placenta. This varies in different cases but is frequently seen by the 65–70th day although in some apparently normal pregnancies this may not occur until the 80–90th day.

While it is believed that the rapidly increasing gonadotropin production is
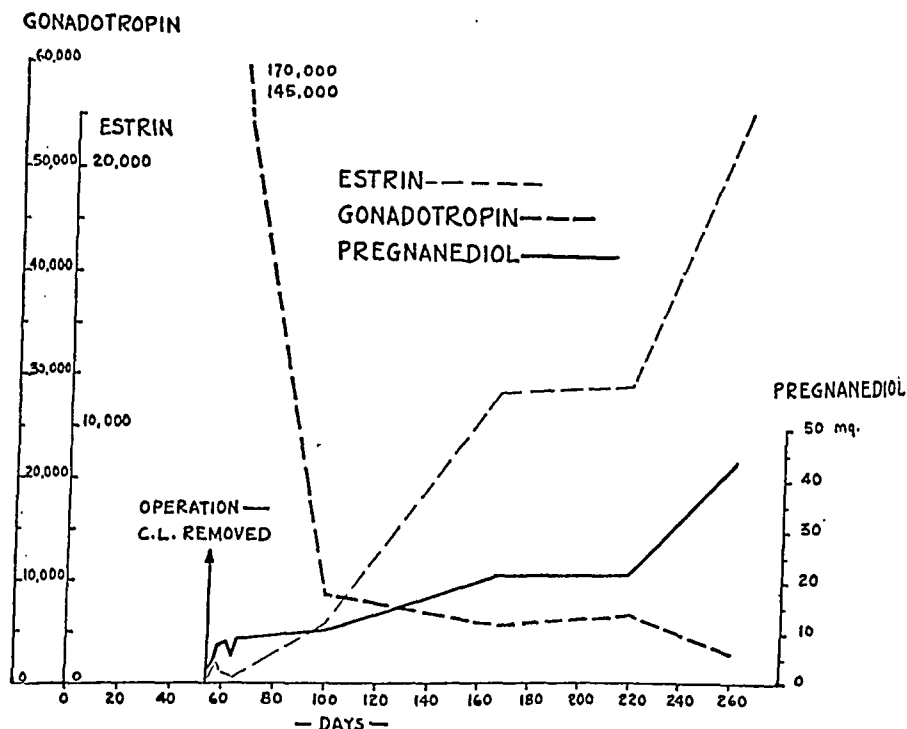
FIG. 5. Excretion of estrogens, gonadotropins and pregnanediol complex in a case where the corpus luteum of pregnancy was removed on the 54th day following the last menstrual bleeding.

necessary for stimulation and maintenance of the corpus luteum, the subsequent equally rapid decrease in this hormone at a time when the placenta is developing and beginning to secrete progesterone and estrogens is not clearly understood. It is probable that the activity and life span of the corpus luteum is determined by the rise and fall of the gonadotropins.

HORMONAL STUDIES ON INDIVIDUAL CASES

The relationship between the various hormones can be more clearly seen when all three are followed in the same individual. Case S. F., Fig. 6. Married 7 years, no previous pregnancies. Assays were carried out throughout the period of conception and at frequent intervals throughout pregnancy. Pregnanediol

was present in the urine on the 14th day. With the appearance of urinary gonadotropins, the pregnanediol excretion increased from 5.7 mg. to 11.3 mg., and was maintained at this level until the 48th day when the urinary pregnanediol decreased to a level of 6 mg. Five mg. progesterone were given intramuscularly from the 54th day until the 80th day. At this time the urinary pregnanediol began to rise. The peak of gonadotropin excretion was reached on the 64th day at a level of 136,000 R.U. per 24-hours. By the 110th day it had decreased to 10,000 R.U. per 24-hours. The estrogen excretion followed closely that of
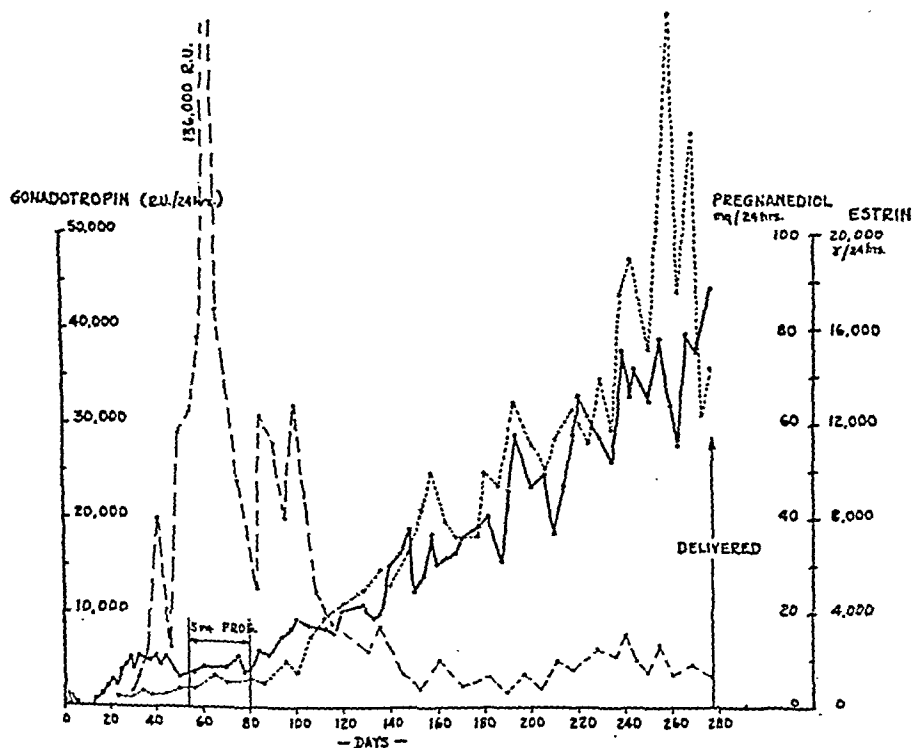
FIG. 6. EXCRETION OF CHORIONIC GONADOTROPINS, ESTROGENS AND PREGNANEDIOL COMPLEX IN A CASE OF NORMAL PREGNANCY

pregnanediol, rising sharply however in the last month. Delivery occurred on the 278th day. No antepartum fall in pregnanediol was observed. Case R. C., Fig. 7. Age 30 years, married 6 years, no previous pregnancies. The urine was collected daily from the 35th day throughout gestation. Assays were carried out either daily or on pooled specimens of 2-3 days. This particular case was used for various metabolic studies. Progesterone was administered on two instances at (1) and (2) with a consequent increase in pregnanediol excretion and at (3) and at (4) aspirin, 5 grams, was given by mouth in order to study its effect on glucuronic acid metabolism. In both instances a rise in glucuronic acid excretion occurred with a simultaneous fall in pregnanediol excretion.

The rise in pregnanediol began in this case around the 70th day, the peak in excretion of gonadotropin occurring on the 68th day. The sharp increase in output of pregnanediol and estrogen on the 195th and 196th day is unexplained. In this case as in the previous one there is a definite rise in the excretion of estrogens in the last few weeks of pregnancy. A cesarean section was done on the 277th day.

FIG. 7. EXCRETION OF CHORIONIC GONADOTROPINS, ESTROGENS AND PREGNANEDIOL COMPLEX IN A CASE OF NORMAL PREGNANCY

The possibility that the ratio of the hormones, progesterone and estrogen, may be of importance as well as the absolute amount of these substances excreted should be considered. In early pregnancy approximately 10 to 20 times as much pregnanediol as estrogen is excreted per unit weight. As the placental function increases this ratio is reduced to approximately 5 to 1. Near term there is usually a marked rise in estrogen excretion reducing this ratio still further.

INITIATION OF LABOR

Little is known regarding the factors responsible for the initiation of labor. Several investigators have suggested it is due to a withdrawal of hormones, that a decrease in excretion of pregnanediol and estrogen occurs during the last few weeks of gestation.   Marked fluctuations in the excretion of the hormones are
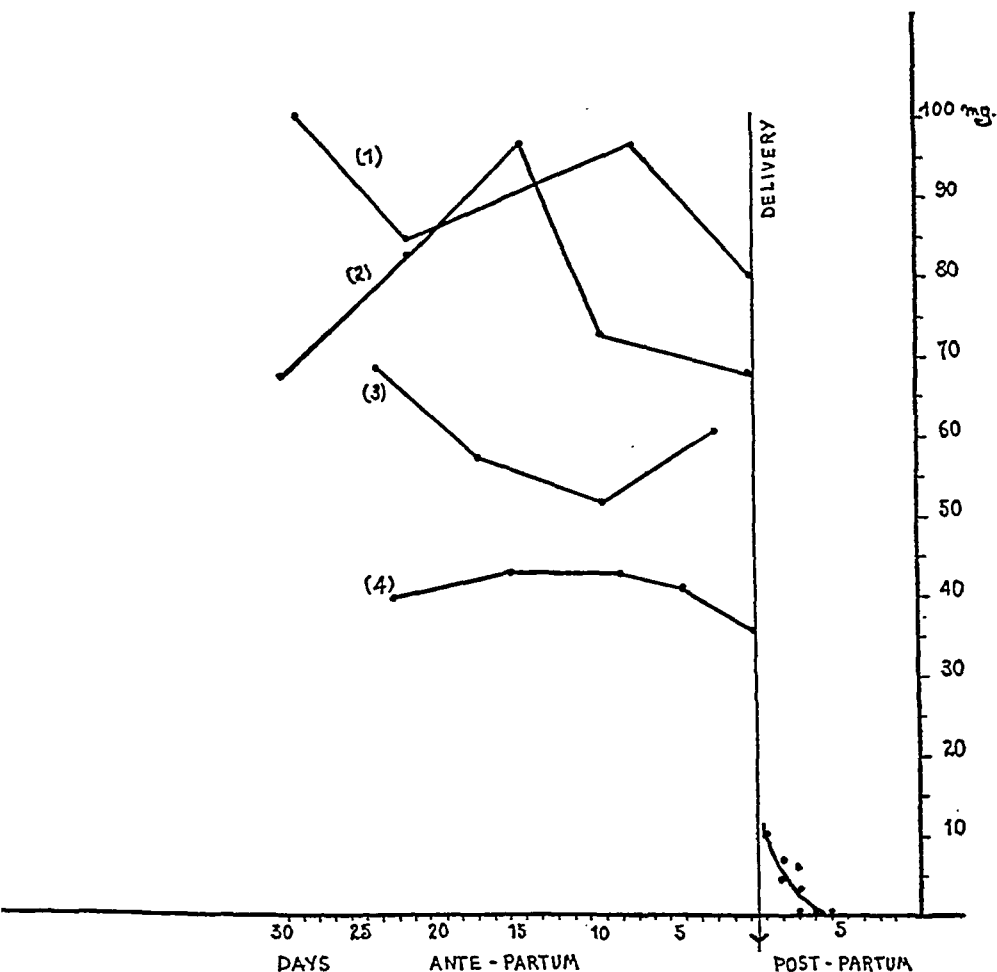
FIG. 8. EXCRETION OF PREGNANEDIOL COMPLEX ANTE- AND POST-PARTUM

observed in the latter part of pregnancy and in many cases where assays are carried out at weekly or even greater intervals, these fluctuations have an appearance of cyclic remissions.   It has been suggested that labor occurs at a time when pregnanediol is decreasing.   We have found that when assays are carried out at more frequent intervals, these cyclic remissions are not so striking and in many instances labor may begin on a rising pregnanediol output.

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studies show that as soon as the placenta begins to separate there is a rapid drop in pregnanediol output but there is no indication that a marked fall in progesterone elaboration occurs several days prior to the onset of labor. The pregnanediol excretion curves of 9 patients who have been closely followed during the last month of pregnancy are shown in Fig. 8 and Fig. 9. In 6 of these cases the urine was collected right up to the onset of labor and in 2 cases throughout labor up to the time of delivery. There is no consistent trend in the excretion
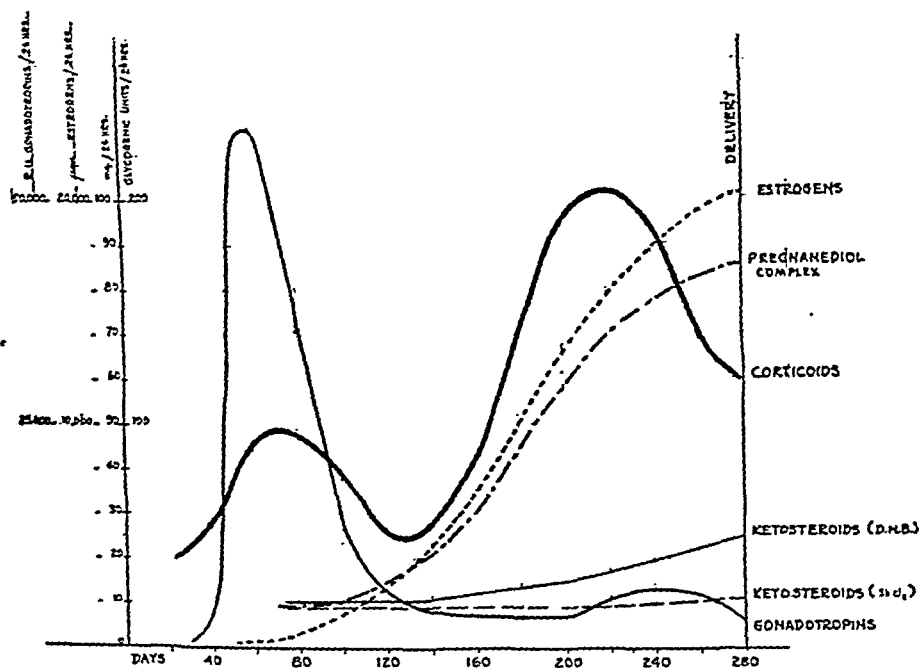
FIG. 10. EXCRETION OF CHORIONIC GONADOTROPINS, ESTROGENS, PREGNANEDIOL COMPLEX, CORTICOIDS AND KETOSTEROIDS IN NORMAL PREGNANCY

of this metabolite and in none of these cases is there a marked fall in output of pregnanediol prior to the onset of labor. With the exception of case 4 and case 9, amounts of pregnanediol found in urine at the beginning of labor ranged from 55 to 105 mg. On the day following delivery 11 mg. of pregnanediol was present in one case and by the fourth day no pregnanediol could be detected in the urine.

ADRENAL HORMONES

Earlier investigators had noted, by direct observation, that the adrenal gland undergoes definite hypertrophy during pregnancy. Recently methods have been developed whereby adrenal activity can be evaluated by the measurement in urine of substances which are derived from the metabolism of adrenal hormones.
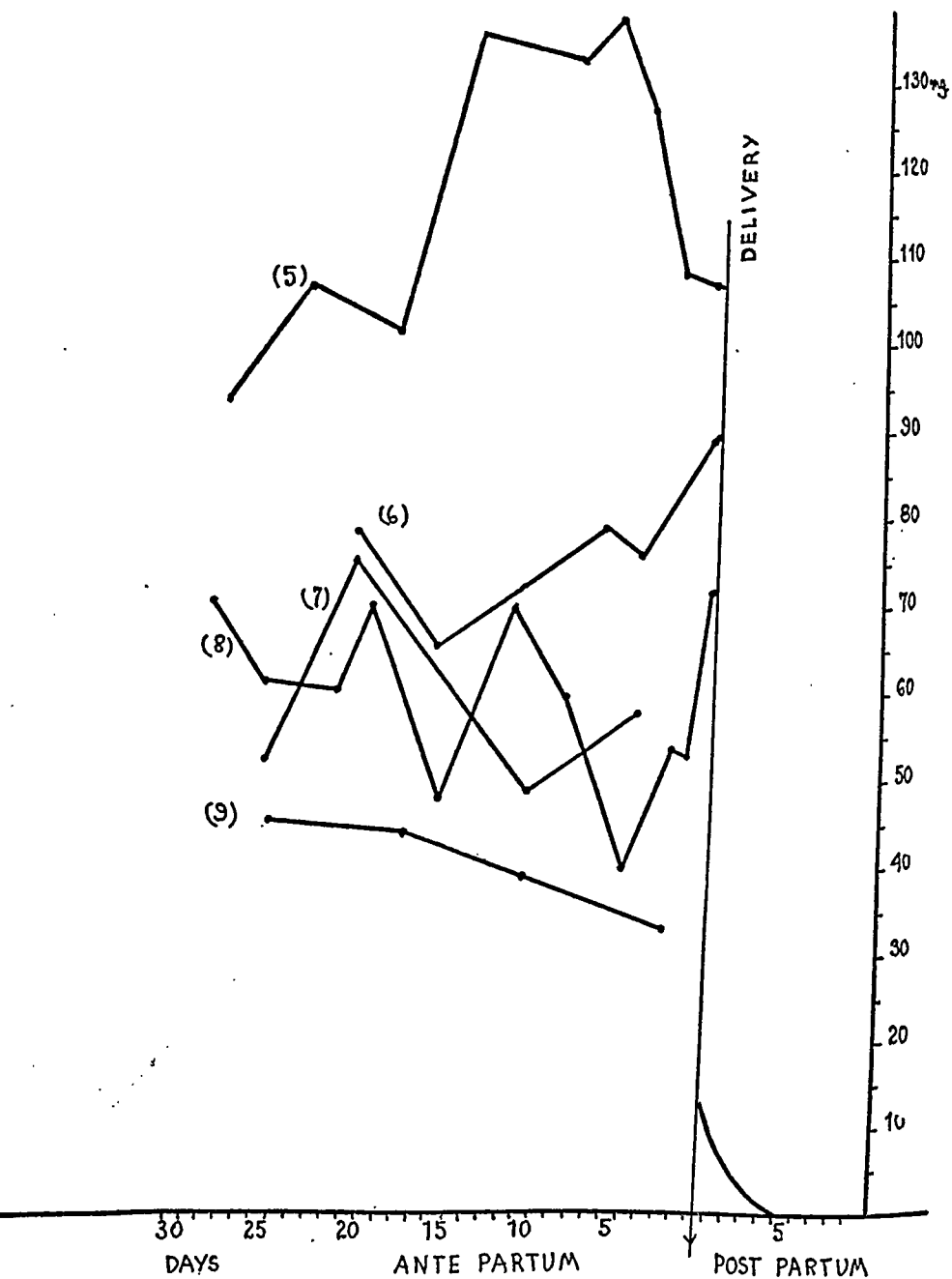
FIG. 9. EXCRETION OF PREGNANEDIOL COMPLEX ANTE- AND POST-PARTUM

It has also been suggested that because of a lag in excretion of these substances changes in secretion of progesterone would not be immediately seen. Our

In two cases where the ovary containing the corpus luteum of pregnancy was removed on the 54th and 98th day respectively, pregnancy continued and the usual rise in estrogen and pregnanediol output was observed.

Studies on the excretion of adrenal corticoids reveal that there is a considerable increase in the output of these hormones in pregnancy, a rise occurring in the first and last trimesters. The significance of these findings is not clearly understood.

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DISCUSSION

DR. A. E. RAKOFF: In the hope of learning a little more about the intermediary metabolism of the steroid hormones during pregnancy, we at the Jefferson Medical College have been interested recently in studying the bile of pregnant women and also of pregnant cows, and for this purpose have collected a rather considerable amount of material by biliary drainage from late pregnancy in women and also from the gall bladders of cows. We have found that there are very important differences in the excretion of these steroid products in the bile as compared to the urine.

For instance, pregnanediol is not present in the bile of women or in the pregnant cow bile, although some similar related metabolites of progesterone may be present. Estrogens are present in goodly amounts in the bile. In fact, they are present in amounts larger than they are in the blood, but not nearly so much as in urine. There is considerable difference however in the form of estrogen in these two species, being present largely in the free state in the cow and largely in the conjugated state in the human.

Dr. Pearlman, who I notice is here, has made some isolation studies of specific compounds from this material and I think that he might have some interesting material to present on the exact compounds which he has isolated from these sources.

CHAIRMAN CORNER: Would Dr. Pearlman like to speak briefly on this point?

DR. WILLIAM H. PEARLMAN: The pregnant cow was selected because bile from this species is abundantly available from the slaughter-house. We have succeeded in isolating the following crystalline compounds from ether extracts of unhydrolyzed bile: estrone, pregnanol-3(alpha)-one-20, pregnanediol-3(alpha),20(beta) and etiocholanediol-3(alpha), 17(beta). These substances occur in quantities ranging approximately from 0.5 to 2 mg. per liter of gall-bladder bile which was obtained from cows at least 5 months pregnant.

The isolation of estrone from bile lends some measure of support to a theory of an entero-hepatic circulation of estrogens under physiological conditions which was suggested by Cantarow and co-workers a few years ago. Pregnanol-3(alpha)-one-20 is now recognized to be a metabolite of progesterone. It is excreted in the urine as well as in the bile during pregnancy. It is curious that whereas pregnanediol-3(alpha), 20(alpha) but not the 20(beta) isomer is excreted in the urine, the latter but not the former is excreted in the bile of the pregnant cow. Etiocholanediol-3(alpha),17(beta) has not been obtained from urine or for that matter from any other natural source material except bile.

Another crystalline substance, Compound X, was obtained from the nonalcoholic ketonic fraction of the bile extracts. Although this substance absorbs light strongly at 240 mμ as

Two groups of adrenal metabolites, the 17-ketosteroids and the corticoids are capable of assay by laboratory methods. While the 17-ketosteroids are considered to be associated with the androgenic function of the adrenal, the urinary corticoids possess the property of affecting carbohydrate and protein metabolism. A study was made by the author (5) of the excretion of these two different types of adrenal metabolites in a series of nine pregnant women and the findings were correlated with the excretion of pregnanediol, estrogens, and gonadotropins. In Fig. 10 average excretion curves of the various hormones are presented.

During the first trimester there is an increased excretion of corticoids above the values found in the non-pregnant woman. After this initial rise, the corticoid excretion returns to normal levels. Between the 140th to 160th days urinary corticoids begin to rise again, reaching in some cases values over 300 glycogenic units. Usually there is a decrease in output in the latter part of pregnancy. These high excretions of corticoids observed in pregnancy are surprising as they are in the order of amounts found in the urine of individuals following severe trauma, or of patients suffering with Cushing's Syndrome. The significance of this increase in adrenal activity is not clearly understood. Little change was noted in the excretion of 17-ketosteroids when the Pincus reaction was used as the method of assay, but when these substances were measured by means of the Zimmerman reaction an increase occurred in the latter part of pregnancy. This was found to be due to the production of 20-ketosteroids such as the pregnanolones which are excreted in increasing amounts in pregnancy and which give a red brick color in the Zimmerman reaction.

SUMMARY

The study of the excretion of urinary metabolites of the ovarian, placental and adrenal hormones has thrown considerable light on the inter-relationship of the various endocrine glands in pregnancy.

Following implantation of the fertilized ovum a definite sequence in events with regard to the excretion of hormones occurs. There is a rapid increase in the output of chorionic gonadotropins which reaches a peak between the 50th and 70th days after the last menstrual period. The pregnanediol complex continues to be excreted either at the same level or slightly higher than those found in the luteal phase. Estrogens are also somewhat increased. Between the 60th and 90th days a definite rise occurs in the excretion of pregnanediol and estrogens. This is associated with the increasing activity of the placenta in the production of these hormones. In the meantime the gonadotropins are decreasing, reaching levels between 5000 and 10,000 R.U. per 24-hours by the 100-120th day. These continue to be excreted at this level up to term although occasionally a rise is seen in the last trimester. The estrogens and pregnanediol continue to be excreted in increasing amounts up to the end of gestation. No consistent changes occur in the output of pregnanediol prior to the onset of labor. The marked decrease in pregnanediol output described by several investigators has not been observed in our studies.

THE URINARY EXCRETION OF KETOSTEROIDS IN PREGNANCY

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We have investigated the steroid excretion by pregnant women as a part of a broad investigation dealing with the metabolism of steroid hormones in healthy and diseased persons. Since we are primarily concerned with the changes in steroid excretion associated with the growth of a malignant process, the alterations in steroid metabolites during a normal pregnancy have provided a valuable index of the adaptation of the adult organism to non-malignant growth. The present results which are to be considered preliminary in nature, have been published briefly elsewhere (1), and are confined to the neutral ketones obtained from urine by methods we have described in detail (2, 3, 4). Infrared spectrometry has been used extensively in our studies, and with the aid of this valuable tool, we have been able to establish the pattern of ketosteroid excretion by the pregnant human female.

As a result of these studies, 19 ketosteroids have been isolated and characterized. Eleven of these, shown in Table I, have been found only in the urine of pregnant women; 3 (Δ^3-androstenone-17, Δ^{3-5}-androstadienone-17, and etiocholanol-3(α)-one-17) have been found both in the urine of pregnant women and of normal subjects. In addition 5 steroids were isolated which had been identified previously in the urine of pregnant women by other investigators. These substances are: isoandrosterone (5); androsterone (6); pregnanol-3(α)-one-20 (5, 7); allopregnanol-3(α)-one-20 (8); and allopregnanol-3(β)-one-20 (9).

In a healthy woman who underwent a normal pregnancy, the urinary excretion pattern of the alpha ketosteroids was studied at monthly intervals beginning at the third month of pregnancy and ending one month postpartum. Five of the most abundant steroids, 3 of which are normally present in all subjects and 2 of which appear in significant amounts only in the gravid female, have been examined in detail. These results are presented in Figure 1, and the contrast between the normal and the pregnant state is immediately apparent. Pregnanolone and allopregnanolone are excreted in considerable amounts during pregnancy; they occur only occasionally in the urine of non-pregnant women. Allopregnanolone seems to be excreted at a relatively constant level of 1 to 2 mg. per 24 hours throughout pregnancy, whereas pregnanolone increases steadily from 3 mg. per 24 hours during the third month to a value exceeding 40 mg. per 24 hours at the ninth month. Pregnanolone parallels the excretion of the pregnanediol complex as reported by Venning (10). Following parturition, the

does progesterone (and other alpha, beta unsaturated ketones), it is not identical with progesterone. The quantity isolated is inadequate for identification.

Our work on bile obtained from pregnant women by duodenal intubation is in a less definitive stage. Suffice it to say that we can detect roughly 4 mouse units of estrogenic activity per ml. of hepatic bile.

In summary: our studies indicate that steroids in the estrogen, progestin, and androgen series are excreted in the bile of the cow under normal physiological conditions, namely, those of pregnancy. Some of these steroid compounds are excreted in the urine as well as in the bile, but certain others appear only in the bile. Thus our knowledge of steroid hormone elaboration and excretion during pregnancy has been extended by including bile in the list of natural source material for isolation work.

steroid excretion promptly returns to the amount and pattern characteristic of the normal woman.

Androsterone and its isomer etiocholanolone, major constituents of the urine of normal women, are excreted in nearly normal amounts during early pregnancy. By the 8th month, however, androsterone has disappeared from the urine and the excretion of etiocholanolone is very much reduced. Both compounds re-appear promptly in normal amounts after delivery. These findings show that during pregnancy, not only are new compounds produced, but alterations in the production of the usual urinary steroid constituents occur in association with and perhaps because of the growth requirements.

The two metabolites of adrenal cortical origin which are regularly present in the urine of non-pregnant women, are 11-keto-etiocholanolone and 11-hydroxy-androsterone. 11-keto-etiocholanolone is excreted in apparently a normal amount during pregnancy, while 11-hydroxy-androsterone is absent from the urine of pregnant women. This points again to an alteration in the production or intermediary metabolism of adrenal cortical precursors, which is part of the adaptation of the organism to the demands of a normal growth process.

SUMMARY

The ketosteroid components in the urine of pregnant women differ quantitatively and qualitatively from those found in the urine of non-pregnant women. These findings are interpreted as evidence that pregnancy induces alterations in the mechanism of production or metabolism of the steroid precursors.

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TABLE I

New ketosteroids excreted in pregnancy

135–136°
Allopregnanedione
Pregnanedione
117–121°
120–125°
235–237°
Allopregnanediol-3α-6-one 20
192–194° $C_{21}H_{34}O_3$
Δ² Allopregnane-3β-one 20
272–275°
209–210° $C_{21}H_{34}O_3$
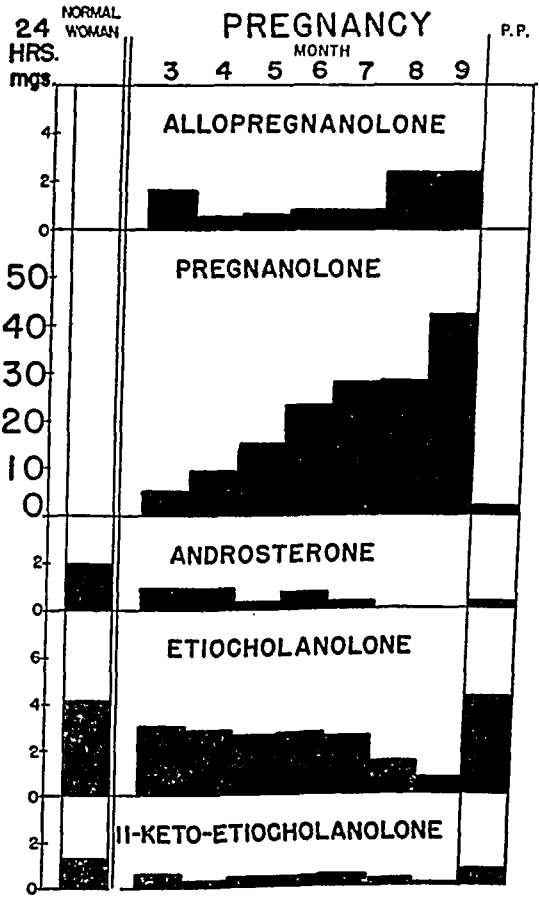
FIG. 1.

for assaying estrogens in the cycle and in early pregnancy were not available. The pathological specimens were examined and classified according to the Carnegie type when completeness of the specimen permitted.

RESULTS AND DISCUSSION

In a previous study of 24 normal pregnancies the range of variation in serum chorionic gonadotropin and pregnanediol excretion was determined. Assay results from the abortion cases have been plotted against the background of these normal curves for evaluation.

A number of .different patterns are found even in this selected group of recurrent abortions and suggest that abortion is by no means a single entity. In some cases more than one possible explanation can be derived.

(Interpretation has been made from the premise that normally the corpus luteum supplies a satisfactory amount of progesterone which will be mirrored by the pregnanediol excretion. The well prepared endometrium implants a normal blastocyst. A flourishing trophoblast secretes increasing amounts of chorionic gonadotropin which stimulates the aging corpus luteum until the trophoblast has raised its own progesterone production to the maintenance level, which probably occurs relatively early.)

The first group of charts (1–4) show what appears to be a trophoblastic failure type of abortion. In each case the pregnanediol excretion suggests adequate progesterone secretion, so that the nidation site should have been adequate. In spite of this the trophoblast was feeble and performed poorly its primitive function of producing gonadotropin. The first two abortions were Carnegie type 1. The next two were somewhat more developed, falling into type 5 and interestingly the chorionic gonadotropin secretion was higher though still deficient.

Charts 5–6 show poor early pregnanediol excretion and inadequate gonadotropin. A poorly functioning trophoblast may have failed to stimulate the corpus luteum to produce progesterone. On the other hand inadequate progesterone may have been the primary fault with resultant blighting of the trophoblast.

The case in chart 7 is one of good early chorionic gonadotropin with borderline pregnanediol. Rapid decline of both values suggests trophoblastic death and prompt abortion of Carnegie 1 type followed.

Chart 8 is uncertain in interpretation. Pregnanediol excretion was ample and chorionic gonadotropin fairly good but the patient suddenly aborted a Carnegie 5 product. This is the only case in the series of an apparently normal endocrine pattern with a low type of defective abortus. The patient had a bicornate uterus and the husband a somewhat deficient sperm picture.

Charts 9–12 are illustrative of some cases in which low thyroid function seemed to be an important factor. The woman whose pregnancies are shown in chart 9 had a 16 year history of sterility and frequent severe functional bleeding from endometrial hyperplasia. During a transitory remission several years previously there had been one pregnancy which aborted at the 5th month. Low

ENDOCRINE PATTERNS IN ABORTION*

ELEANOR DELFS AND G. E. S. JONES

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Johns Hopkins Hospital*

This study was begun with the purpose of finding whether deviations from the normal endocrine pattern were associated with pregnancy terminating in abortion.

In attempting to reconstruct the sequence of events preceding abortion a pregnancy must be studied from its inception since it is obvious that any variation in the fetal environment is of paramount importance in the early stages of development. Since only 10 per cent of all pregnancies end in spontaneous abortion, selecting women for study at random would yield very few abortions. For this reason the study of incidental abortion was considered impractical. It seemed more feasible, therefore, to study pregnancy in women with habitual abortion or some known reproductive difficulties. Such selection immediately precludes the application of the data to the problem of incidental abortion in general. In the material presented here, there is reason to expect recurrent factors to have a dominant role.

MATERIAL

Seventy-nine pregnancies were studied and 30 terminated in abortion. Of these abortions 25 represented at least the third consecutive abortion (in 15 of them the 4th to 8th abortion); 3 of the remaining abortions were 2nd abortions in women with histories of marked reproductive abnormality and the other 2 were first abortions in normal women, these being the only incidental abortions in the series.

METHODS

All of these women were studied as completely as possible and the husbands' semen was evaluated when obtainable. Medical and obstetrical history and examinations were carried out; laboratory study included blood and urine examinations, serological test for syphilis, Rh determination and serum vitamin E. In order to assess the endocrine status, blood sugar, cholesterol and basal metabolic rate were done. Specific reproductive endocrine studies included repeated determinations of urinary pregnanediol in the cycle and throughout pregnancy, and repeated determinations of serum chorionic gonadotropin throughout pregnancy. The methods used were developed and standardized in our laboratory and have been reported elsewhere. Data from the abortion cases were evaluated by comparison with the curves established for these metabolites in normal pregnancy. At the time these studies were begun, adequate methods
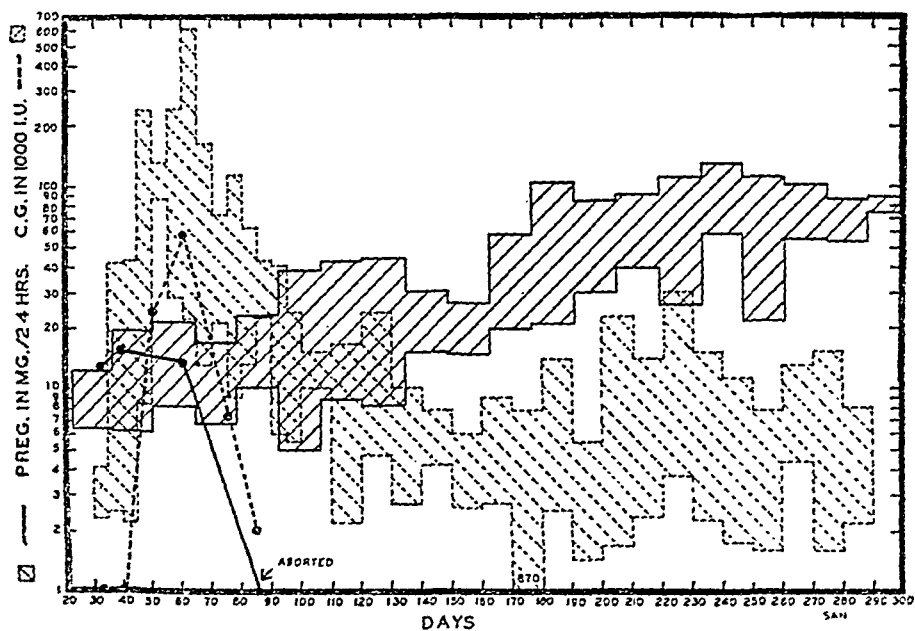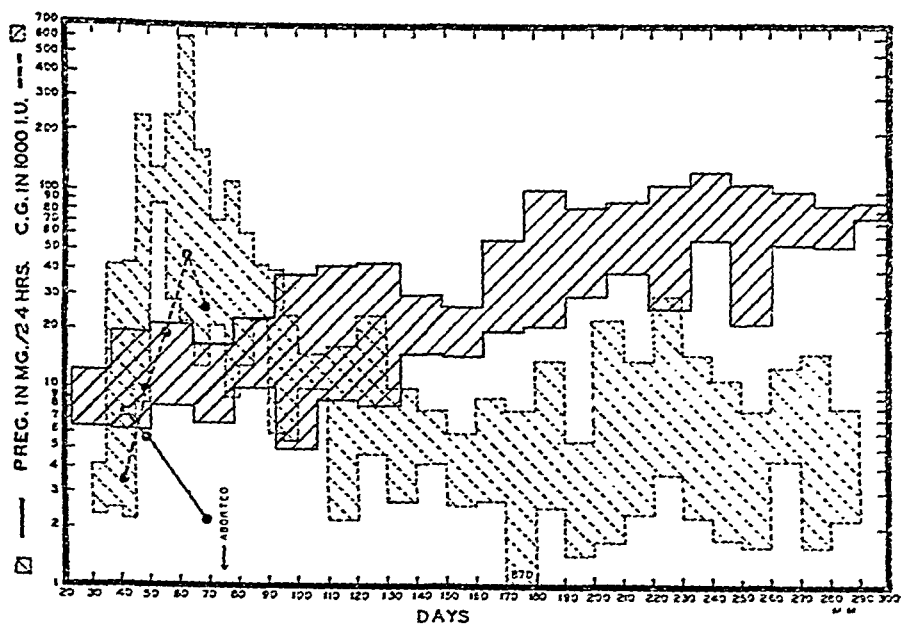
FIG. 3

FIG. 4

FIG. 3 & 4. "TROPHOBLASTIC FAILURE." CARNEGIE TYPE 5 ABORTUS IN EACH
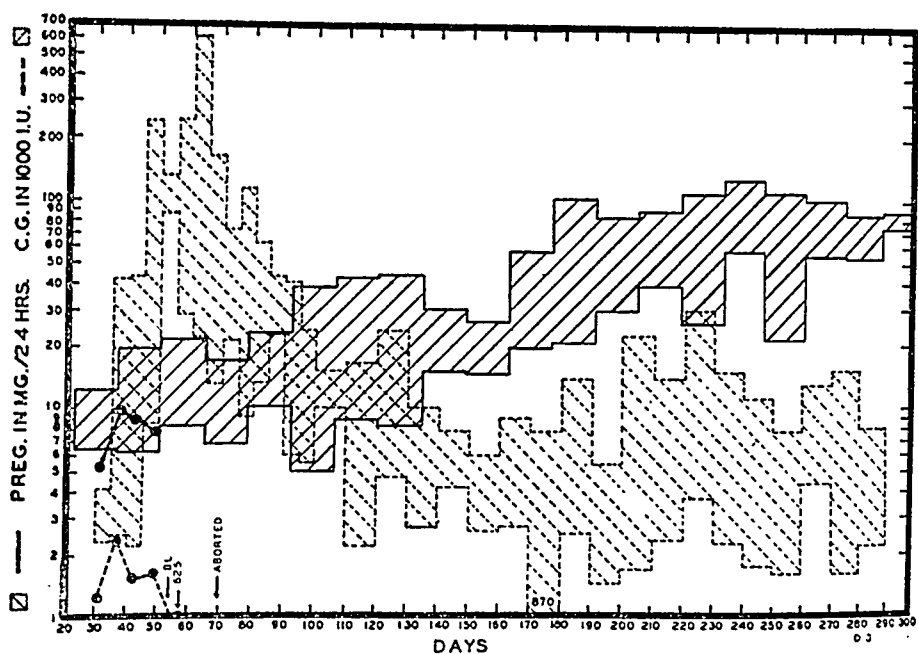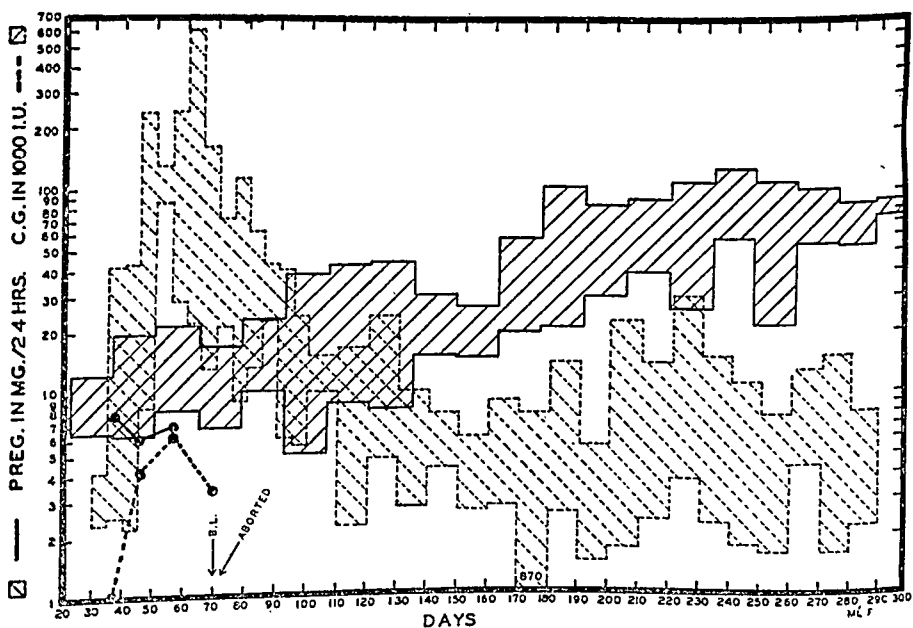
FIG. 1 & 2. "TROPHOBLASTIC FAILURE." CARNEGIE TYPE 1 ABORTUS IN EACH

Serum chorionic gonadotropin and urinary pregnanediol in pregnancies ending in abortion.

The broken lines show chorionic gonadotropin in thousands of I.U. per liter of blood and the solid lines the pregnanediol excretion in mgm. per 24 hours. Block charts in the background give the range of gonadotropin (broken line hatch) and pregnanediol (solid line hatch) found in normal pregnancies. Values are plotted on a semilogarithm scale against the day of pregnancy reckoned from the first day of the last menstrual period. This method of presentation applies to the subsequent graphs.

682
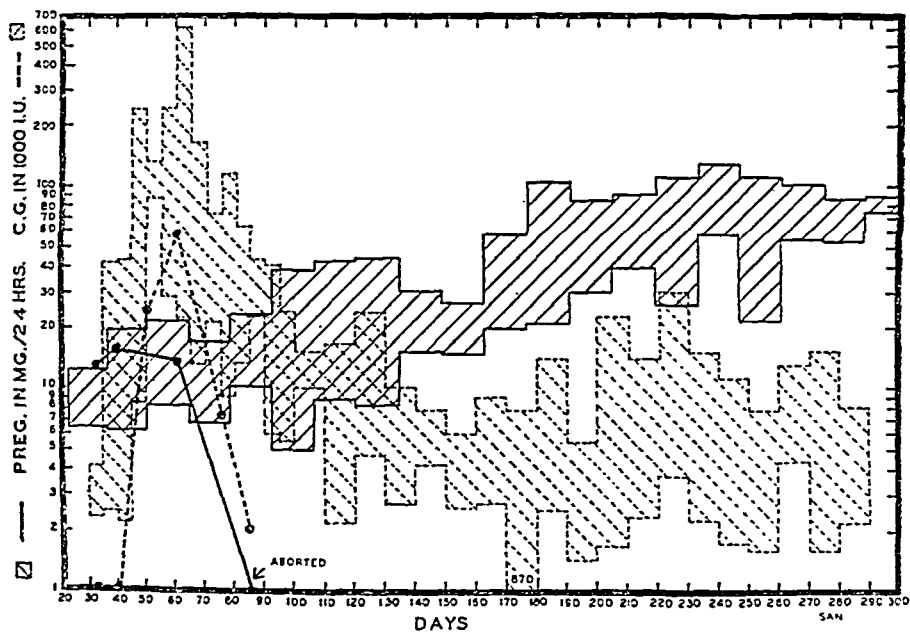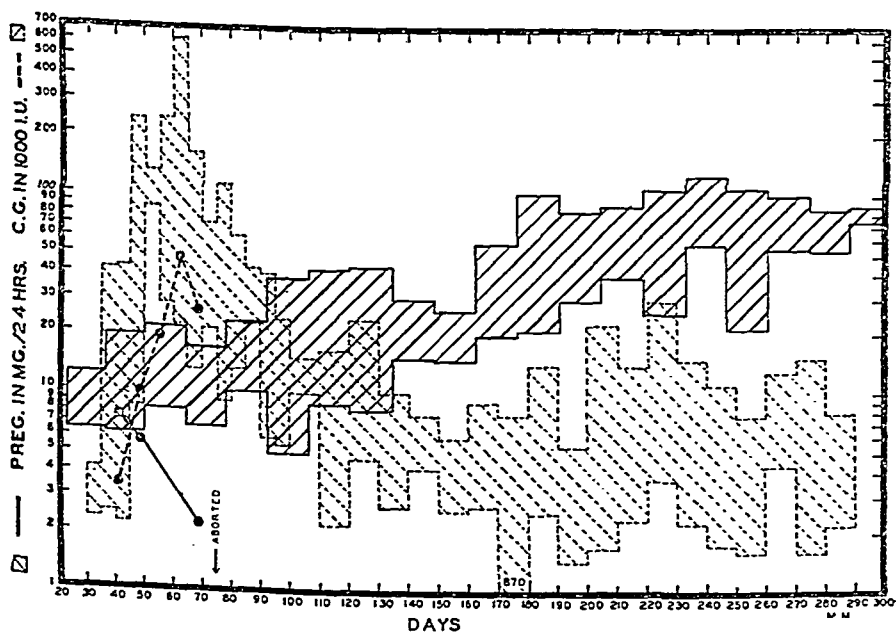
FIG. 3

FIG. 4

FIG. 3 & 4. "TROPHOBLASTIC FAILURE." CARNEGIE TYPE 5 ABORTUS IN EACH

Fig. 5
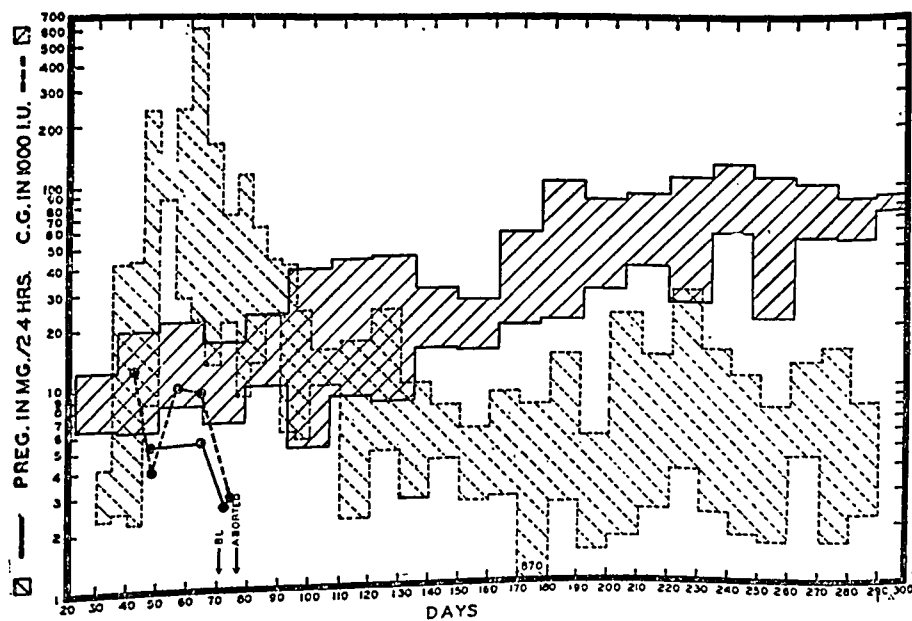
Fig. 6

FIG. 5 & 6. BOTH GONADOTROPIN AND PREGNANEDIOL ARE LOW.   CARNEGIE 1–3.
POOR TROPHOBLAST OR PRIMARY CORPUS LUTEUM DEFICIENCY
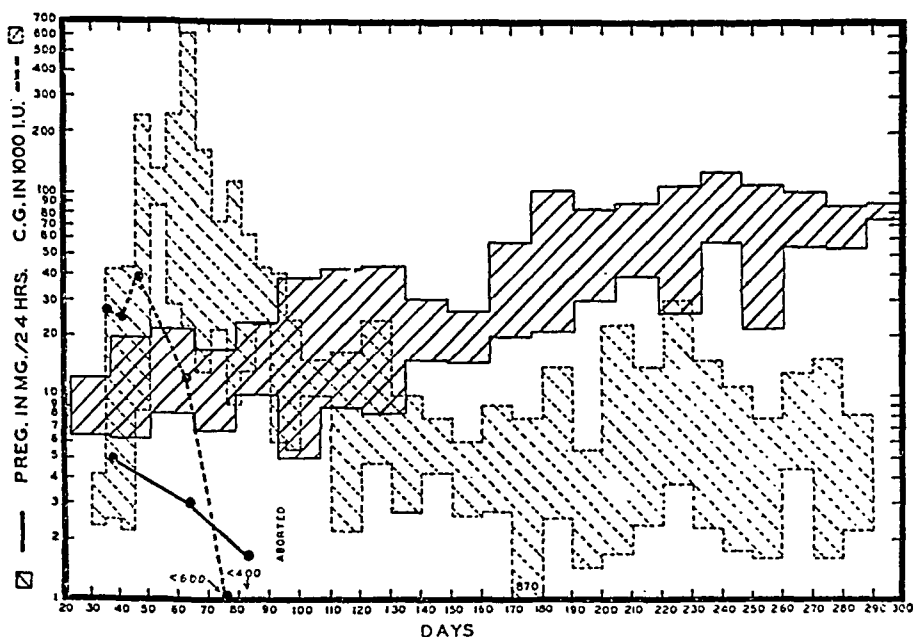
FIG. 7. PROBABLE EARLY DEATH OF TROPHOBLAST
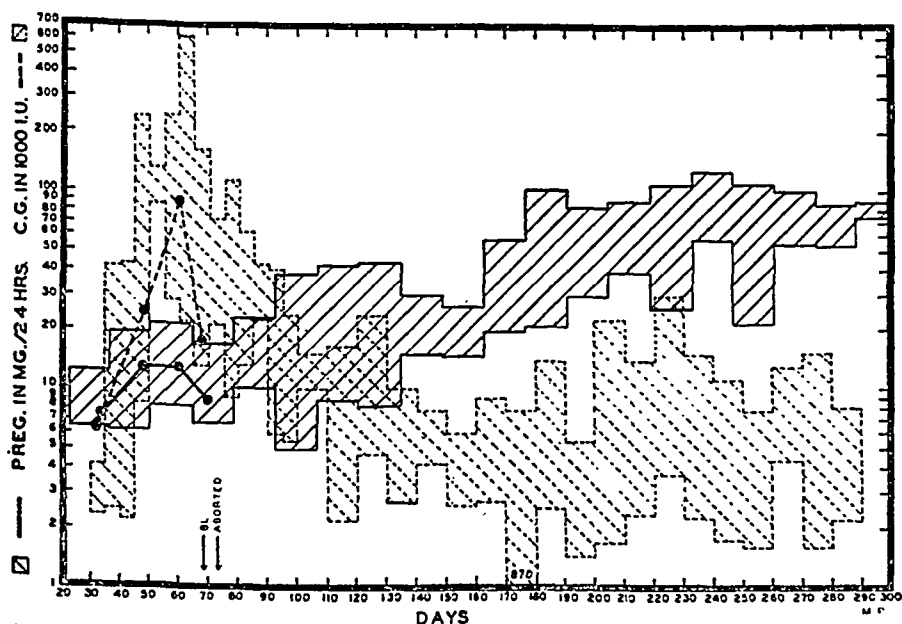
FIG. 8. UNUSUAL FINDING OF NORMAL HORMONE VALUES WITH POOR CONCEPTUS.
CARNEGIE TYPE 5

thyroid function was found and was treated with hope of improving the bleeding.
Pregnancy occurred in less than 2 months and ended in abortion of Carnegie 1
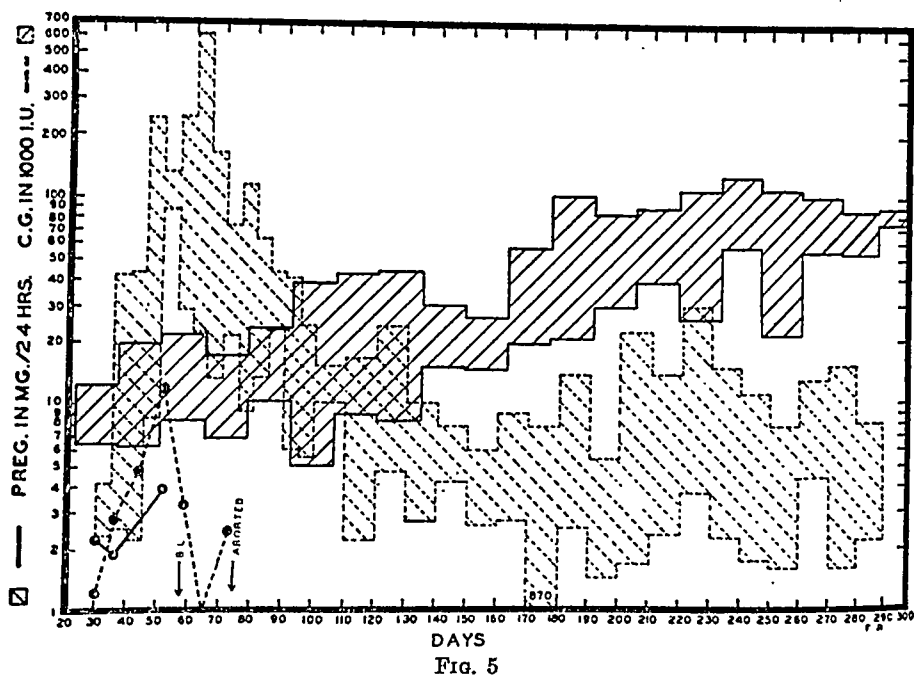
Fig. 5
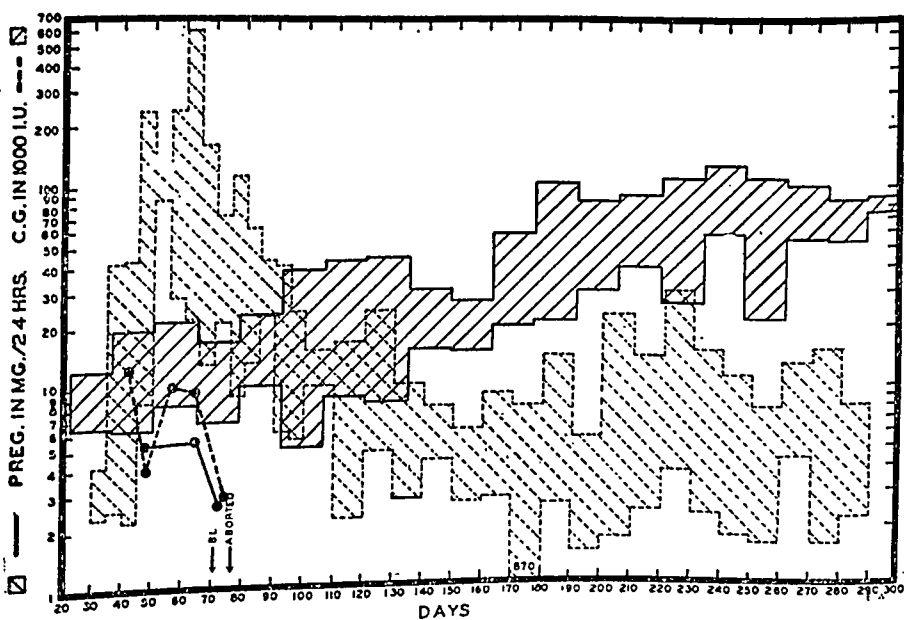
Fig. 6

Fig. 5 & 6. Both Gonadotropin and Pregnanediol are Low.   Carnegie 1–3.
Poor Trophoblast or Primary Corpus Luteum Deficiency
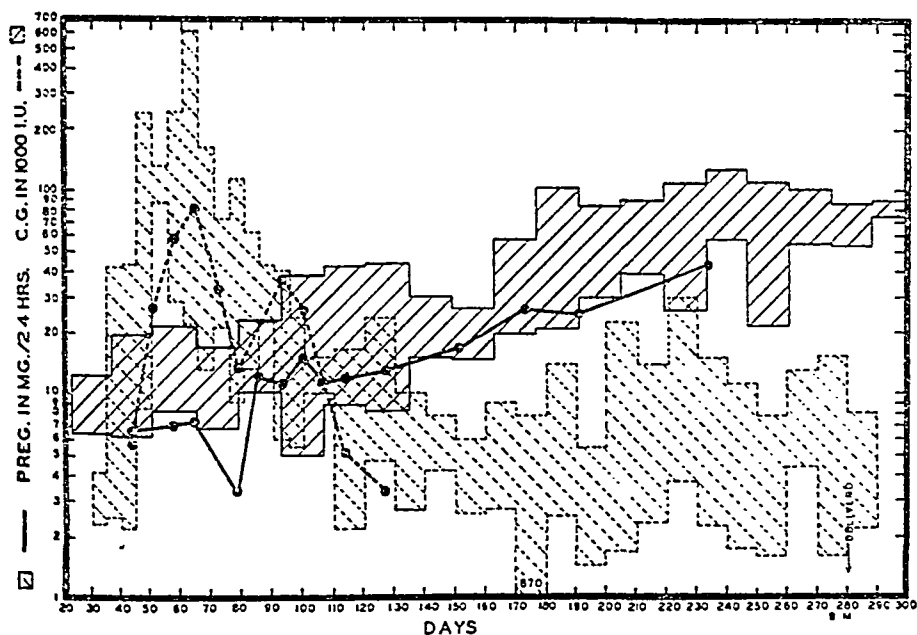
FIG. 11. BORDERLINE PREGNANEDIOL VALUES IN A LOW THYROID CASE (TREATED)
WHICH WENT TO TERM
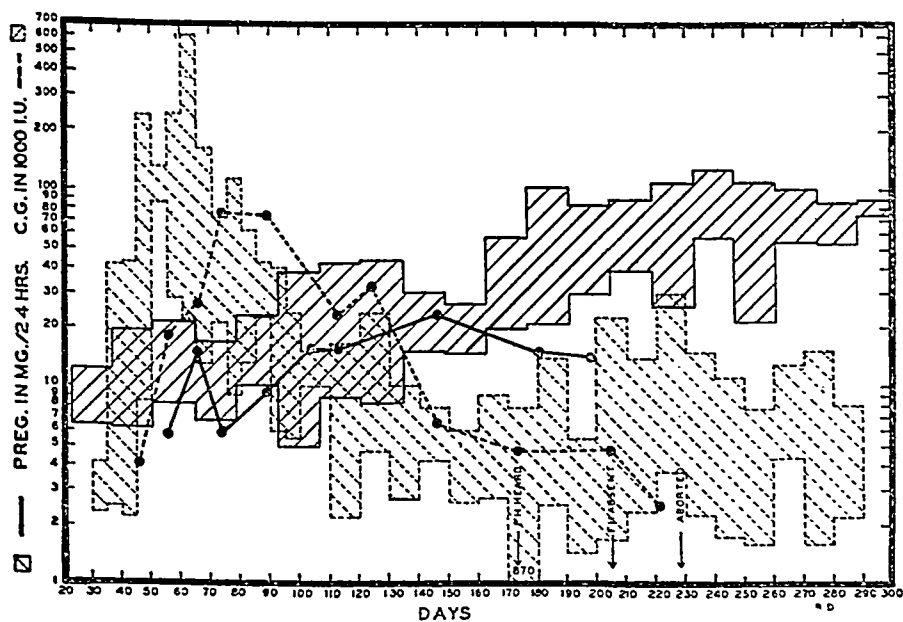
FIG. 12. LATE PREGNANEDIOL DECREASE. MACERATED NORMALLY FORMED FETUS

type.   Pregnanediol and chorionic gonadotropin had been low.   After several
months more of thyroid therapy and normal cycles pregnancy was undertaken.
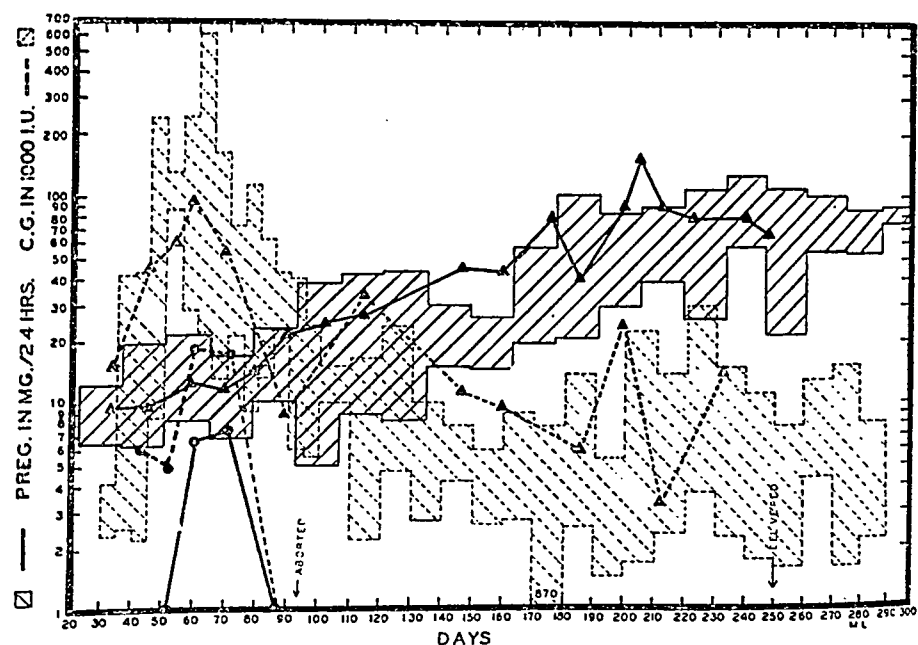
FIG. 9. Circles show values for the third consecutive abortion of this patient. Carnegie 1. Triangles chart the fourth pregnancy which was begun after thyroid therapy and went to term.
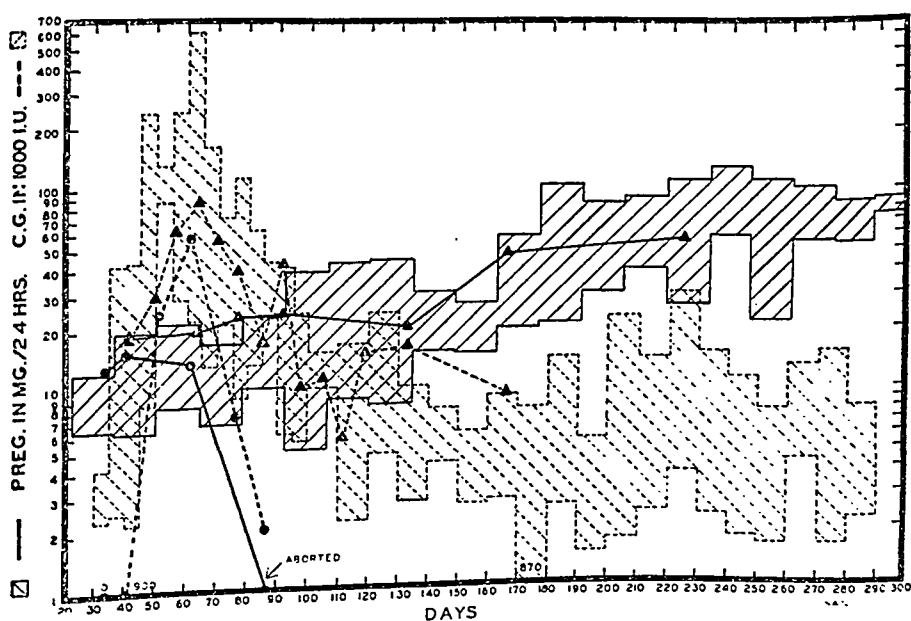
FIG. 10. Circles show values for third consecutive abortion of this patient. Carnegie type 5. Triangles chart the fourth pregnancy which went to term with thyroid therapy.

In the remaining cases (Table 1, 21–30) chorionic gonadotropin levels were consistently normal and the fetuses normally formed, the gestation often carrying to an advanced stage. Pregnanediol excretion was initially normal but late decrease occurred in several cases. Low thyroid function was present in several and at least one case classified as questionably normal became hypothyroid

TABLE 1

Endocrine and pathological findings in 30 abortions

CASES	CHORIONIC GONADO-TROPIN	PREGNANEDIOL	THYROID	SPERM	PATHOLOGICAL SPECIMEN CLASSIFICATION
1	L	L	N	—	Carnegie 1–3
2	L	L?*	N	L	Carnegie 1–3
3	L	L*	L	N	Carnegie 1–3
4	L	L	L		No specimen—resorption
5	L	L	L	—	Degenerating decidua
6	L	L*	L*	—	Carnegie 1–3
7	L	L	L	—	Carnegie 1–3
8	L	N → tL	N	L	Carnegie 1–3 Hydat. degen.
9	L	N	L*	N	Carnegie 1–3
10	L	N	L*	N	Carnegie 1–3
11	L	N	N	—	Carnegie 4
12	L	N → tL	L*	N	Carnegie 5
13	L?	N	L	—	Carnegie 5
14	L	N → tL	?	N	"Immature placenta." Fetus?
15	L	N → tL	L	—	Carnegie 6, 5 weeks
16	L	tL	L	—	Carnegie 6, 6 weeks
17	L?	N	L	N	Carnegie 7, 13 weeks
18	L	L → N*	N	N	Carnegie 7, 9 weeks
19	N	L	—	—	Grossly malformed—18 weeks
20	N	N	N	L?	Carnegie 5
21	N	N	L	—	Carnegie 7, 12 weeks
22	N	N?	N?	N	Carnegie 7, 15 weeks
23	N	N → L	—	L	Carnegie 7, 20 weeks
24	N	N → L*	L*	L → N	Carnegie 7, 26 weeks
25	N	N → L	N	N	Live fetus, 27 weeks
26	N	N	L*	—	Carnegie 7, 30 weeks
27	N	N → tL	N	—	Live fetus—28 weeks
28	N	N	N?	—	Carnegie 7, 22 weeks
29	N	N	N	N	Carnegie 7, 20 weeks
30	N	N	N	—	Carnegie 7, 14 weeks

Key: L—Low, tL—terminal low, N—normal, *—treated

later. (It is possible that lesser degrees of thyroid deficiency existed in others of this group of patients permitting a more advanced gestation but rendering diagnosis difficult.)

A summary of data on the entire group of women with reproductive difficulties is shown in Table 2. Such a tabulation is an over-simplification but emphasizes some trends. The first column gives the occurrence of deficiencies in the preg-

Chorionic gonadotropin and pregnanediol were both normal as the chart shows and the pregnancy went to term.

The patient in chart 10 had had 2 previous abortions at 3 months. The third abortion (charted here) showed excellent pregnanediol values. Early gonadotropin values were very poor, later rose to normal, only to drop precipitously again, followed by a Carnegie type 5 abortion. A demonstrated thyroid deficiency was then corrected and several months later the 4th pregnancy was begun. Assays showed excellent levels from the beginning and a normal infant delivered at term.

Chart 11 is that of a woman whose 4 pregnancies had all ended in abortion at 3–6 months. Hypothyroidism was found and treated for 2 months before pregnancy began. The gonadotropin curve was normal. Pregnanediol excretion remained on the borderline of normal but pregnancy continued to term.

Illustrated in chart 12 is the 6th pregnancy of a woman who had had 5 proven abortions at 2 months in a 3-year period. Definite thyroid deficiency was found and treated for 3 months before pregnancy. Chorionic gonadotropin secretion was very good and pregnanediol excretion within the normal range. At the 26th week the pregnanediol fell slightly and shortly afterward the fetal heart was absent. Three weeks later a macerated, normally formed fetus was expelled. In retrospect it seems likely that this represented a metabolic failure probably due to inadequate thyroid therapy.

Various individual charts have been shown to demonstrate some of the patterns seen. Table 1 gives the data on the individual cases of the 30 pregnancies ending in abortion. Arrangement of cases has been made in a general way in the order of decreasing abnormality of the endocrine pattern and pathological type. It is striking at once that in the first cases (1–10) low chorionic gonadotropin was found in every one and was always associated with a poor conceptus in the Carnegie 1–3 types. Pregnanediol excretion and thyroid function were low in almost all of these also. The first case (1) represents an incidental abortion in a normal woman who had no reproductive difficulties before or after this abortion. (This was probably a poor ovum or defective implantation of the sort Dr. Hertig has emphasized.) One other such case is included in the 30 abortions (11). Two other cases (2 and 8) warrant comment in that both had normal thyroid function but in each the husband's sperm picture was deficient, which may have been a factor in the poor product of conception.

Continuing through Table 1 (11–20) low chorionic gonadotropin persisted though in general the values were not as low as in the preceding cases, pregnanediol values approached normal frequently, low thyroid function was still a frequent occurrence. The products of conception were defective but more advanced in development than formerly. Two cases should have special comment; (case 18) was the only case in the series with definitely poor trophoblastic function and apparently normal fetal development; (case 20) was unique with normal endocrine pattern throughout associated with a pathological conceptus (as mentioned previously this woman had a bicornate uterus and her husband a somewhat deficient sperm picture).

the rat.   Linkage of the thyroid with steroid hormone metabolism would bring together otherwise seemingly unrelated data.   It would also dispose of a troublesome theoretical problem, namely, how the trophoblasts of successive fetuses happen to fail repeatedly in habitual abortion.   Such recurrent failure is explained logically on the basis of a maternal metabolic fault.

CONCLUSIONS

A study has been made of the endocrine patterns and pathological specimens found in 30 abortions which occurred in women who had had reproductive difficulties.   A number of different patterns have been described.   From these patterns some generalizations may be made.

Low chorionic gonadotropin levels were associated with a pathological conceptus or a dying trophoblast and were always followed by abortion.   Normal chorionic gonadotropin, however, did not always preclude abortion.

Early low pregnanediol excretion was often associated with low chorionic gonadotropin and a pathological conceptus and abortion followed.   Whether early low pregnanediol values are compatible with continuing pregnancy cannot be stated, but such a situation must be uncommon as it did not occur in the present series.   Early normal pregnanediol excretion occurred occasionally with low chorionic gonadotropin and a pathological conceptus, so that normal corpus luteum function did not preclude abortion.

Low pregnanediol excretion was seen late in a few cases associated with normal chorionic gonadotropin and normally developed fetus suggesting a late placental failure of steroid hormone production.

Low thyroid function occurred with low chorionic gonadotropin and low types of pathological conceptus with significant frequency.   It was found also in some cases with normal chorionic gonadotropin and higher types of conceptus with late abortion.   It is suggested that thyroid function may be the major factor in the etiology of recurrent abortion and that its importance is likely to increase as more sensitive tests are applied.   The mechanism of its function demands investigation.

DISCUSSION

DR. ARTHUR T. HERTIG: I would like to take this opportunity to congratulate Dr. Delfs and Dr. Jones on this splendid paper, the first one to my knowledge in which there has been any attempt to correlate the clinical, endocrine and pathologic aspects of the abortion problem. This lack of correlation seems to me to have been the great defect in all the literature on abortion.

Dr. Delfs has brought up the problem as to whether the trophoblast or the corpus luteum was primarily defective in the abortions she has studied.   Dr. Rock's and my small series of pathological ova which were found prior to the first missed period and reported here last year, would tend to indicate that of the ova which were grossly bad and obviously destined to abort some time in the future, all appeared to have good associated corpora lutea on the basis of any ordinary histological or pathological criteria that could be applied to them.

The second point on which we have some data, namely the mechanism of successive abortions, has been investigated by Dr. Roscoe Wall and myself in the Pathological Labo-

nancies ending in abortion. Low chorionic gonadotropin was the most common deficiency with low thyroid and low pregnanediol following; the three were frequently but not always coexistent. The second column shows the findings in 49 pregnancies which went to term. The most striking fact here is that not a single case showed low chorionic gonadotropin. It seems clear that low chorionic gonadotropin is incompatible with successful pregnancy. Low thyroid was by far the commonest deficiency in this group. All of the low pregnanediols occurred in low thyroid cases. Therapy is outside the scope of the present discussion but in considering the possible etiological role of the various factors, cognizance must be taken of the fact that in the successful pregnancies the deficiencies found had been eliminated by the appropriate therapy in every case. Many of these low thyroid women had treatment some months preceding pregnancy.

TABLE 2

Data from 79 pregnancies in women with previous reproductive difficulty

DEFICIENCY DEMONSTRATED	ABORTIONS—30	LIVING INFANTS—49	TOTAL—79	OCCURRENCE AS SOLE DEFICIENCY
Low Chorionic Gonodotropin.	18	0	18	1
Low Pregnanediol...........	13	8*	21	4
Low Thyroid................	15	29*	44	25
Low Vitamin E.............	5	6*	11	3
Low Sperm.................	5	0	5	0
Bicornate Uterus...........	2	0	2	1
No deficiency found........	3	16	19	—

* Treated.

The columns showing total incidence of deficiencies and the occurrence of the various factors as the sole deficiency emphasize the frequency of inadequate thyroid function. Several lines of evidence indicate that this is not an incidental finding. Correlation of low thyroid function with low Carnegie type points toward a relationship. Thyroid deficiency increases with the severity of the reproductive derangement, being 37 per cent in cases with less than 3 abortions and 70 per cent in true habitual aborters with 3 or more consecutive abortions. Study of individual cases, their past histories and response to therapy suggests that thyroid function may be more important in the late abortion or premature birth than has yet been clearly shown. Proof of this impression awaits the application of more sensitive methods of evaluating thyroid adequacy, especially directed to study during pregnancy when relative thyroid deficiency may be masked by pregnancy itself when such tests as basal metabolic rate or blood cholesterol are used.

The mechanism by which inadequate thyroid function may produce abortion is not clear. A lead may lie in the work of Engle which showed lowering of the estrogen threshold in thyroidectomized monkeys by administration of thyroid and the work of Weichert relating progesterone metabolism and the thyroid in

Morning Session, Saturday, January 31, 1948
Dr. Nicholson J. Eastman Presiding

EXPERIMENTAL STUDIES ON NUTRITION IN PREGNANCY

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Whether the diet of the mother can influence the development of the fetus is still a controversial question. It was thought and taught until recently that mammalian fetuses and embryos grow and develop as parasites in the maternal organism and obtain the required nutritional elements from the mother's body unless the maternal tissues are completely exhausted. In the latter case, it was said, the fetus dies but as long as the mother is in a fair nutritional state, her diet should not influence the unborn young.

Is this thesis tenable in the light of recent experimental and clinical observations or should we revise our previous conceptions? Fortunately, the subject assigned to me, which concerns the *experimental* studies on nutrition in pregnancy, has been thoroughly studied and a wealth of facts are available for the illustration of some of the points which I like to emphasize and which may help in the discussion of this morning's program. Needless to say, this report does not cover the entire field and the illustrations are arbitrarily chosen.

It is obvious to anyone who works with animals, farmer and investigator alike, that reproductive failure can result from quantitative and qualitative deficiencies of the mother's diet. Sterility, resorption or abortion of the fetus, stillbirth, prematurity, prolonged gestation and weakness of the offspring can be caused by dietary nutritional deficiencies. This list contains various degrees of reproductive failure. The severest degree is sterility while the birth of weak offspring represents a milder form. The list is not complete. For instance, prenatal malformations are not included in this list, which does not represent a classification from a morphologic point of view. Malformed embryos may end in resorption, abortion, stillbirths, premature births or debility of the offspring. The birth of mature offspring with congenital defects represents a relatively high degree of reproductive performance.

Starving animals do not reproduce. If mature female rats are starved their estrus cycle stops and ovulation ceases. *Barry* has shown that starvation begun soon after mating results in resorption of the embryo. Starvation begun after the eleventh day of gestation does not, as a rule, interrupt pregnancy but the litters are reduced in size, about one third of the young are stillborn and their birth weight is reduced by 40 per cent (1).

Deficiencies in single factors may also result in reproductive failure. There is a great deal of experimental evidence that a lack of the following nutritional elements influences adversely mammalian reproduction.

The entire spectrum of reproductive failure from sterility of the mothers to

ratory of The Boston Lying-in Hospital. Approximately 2500 abortuses have been examined by Carnegie criteria in the last 13 years. From this material 100 patients were selected who had had 2 or more successive abortions and whose conceptuses had been examined in our laboratory. The results of this study may be simply stated in that successive abortions tend to repeat their etiology in approximately 60% of the cases. Moreover, these habitual aborters miscarry because of reasons as varied as those of the chance or casual aborter.

DR. MILLEN: The thyroid problem prompts me to state that some time ago I took some daily basal metabolisms on women, ran them the day before and through the whole cycle. They were taken at home under ideal circumstances and all through the variations were so wide that I would hesitate to use the basal metabolism as a very fine indication of the need for thyroid.

DR. M. C. CHANG: With regard to Dr. Hertig's comment, I would like to say that there are several factors in the early degeneration of fertilized eggs. For instance, there are the hormonal, bad eggs, pathological. There is one point that the good eggs may be transported to the uterus too early. In this case, the fertilized eggs in an early stage may not be ready to survive in the uterus or the physiological condition of the uterus is not good for the development of eggs at an early stage. When I transplanted one-day rabbit eggs to the oviducts of does ovulated one day previously, I got 60 per cent normal development. When I transplanted four-day eggs into the uterus of does ovulated four days previously, I got 40 per cent normal development. When I transplanted one-day eggs to the uterus of does ovulated one or three days previously, I got no normal development. That means if the good eggs are transported to the uterus too early they will degenerate. Therefore it may not only be a bad egg or a hormonal defect or pathological, but it also depends upon the time of transportation from the oviducts to the uterus.

We know that we get a large number of eggs degenerated in the pig and we know that fertilized eggs in early stages are found in the uterus of pigs.

DR. MARIE WARNER: One aspect of this problem which is very important to me is the time which should be advocated before granting a second pregnancy. I don't know whether there were any facts on that in the study just reported. The patients usually want to know how long they must wait before they can start a second pregnancy.

If we could use these hormonal tests in some way to help us determine the favorable time, I think we would gain something in our clinical medicine.

DR. EPHRAIM SHORR: Could I ask whether the types of low thyroid cases which were studied in this series required thyroid replacement therapy or was iodine satisfactory?

DR. ELEANOR DELFS: With regard to Dr. Hertig's statement about the type of ovum, of course we are not dealing with "Hertig ova," except perhaps in 2 cases. From statistical expectation we may have happened to get 1 or 2 more incidental abortions.

The study of the Hertig type of ovum, where there is a very early failed pregnancy, would be extremely interesting but almost impossible from the standpoint of practical approach to determine which patient to study. Obviously the patient must be studied as soon as she becomes pregnant and the chance of choosing one who will abort is small.

Concerning tests for the thyroid function, we recognize that the basal metabolic rate and the cholesterol are exceedingly inaccurate. Dr. Peters' work is extremely interesting from that standpoint, because that will add a much better tool. I believe the evidence we have that the thyroid function is an etiological factor is circumstantial to a degree.

In regard to the question about the time of therapy, here again we cannot be very certain about the optimal duration of treatment before allowing another pregnancy. We have a feeling that probably 3 or 4 months is the minimum, but this is just an impression and is not corroborated by specific data.

The patients that we treated all got thyroid rather than iodine.

the mother is not visibly affected. *Davis and Madsen* (5) have shown that cattle may remain apparently healthy as long as their carotene level remains above 25 micrograms and their vitamin A level above 16 micrograms. However, such levels, sufficient for maternal health, may result in disaster to the offspring.

Maternal borderline deficiencies in vitamin A can produce structural defects in the young. *Hale* (6, 7) in 1933 fed gilts of known stocks a deficient diet for 150–200 days before breeding. The same diet was continued during the 30 days after conception when the formation of the eye is completed in the pig. After this stage the maternal diet was supplemented by cod liver oil in order to make sucessful termination of pregnancy possible. The offspring were blind owing to anophthalmos or microphthalmos. They also had accessory ears, cleft lip and palate, subcutaneous cysts, and misplaced kidneys. Since these deformed young survived, Hale was able to mate abnormal sons to their mothers or to their sisters and he could show that in his experiments genetic factors can be ruled out as the cause of the malformations.

Miss Schraffenberger and I (8) were able to induce malformations in the offspring of female rats raised on a diet poor in carotene and vitamin A and bred on a diet completely free of these vitamins. The fertility of such rats is low and the young born do not survive. They are somewhat reduced in size, appear edematous and have frequently subcutaneous hemorrhages. Sometimes they have "open eyes" owing to defects of the lids. In about 78 per cent anomalies of various ocular structures are shown in histologic sections. The most frequent anomaly is a retrolenticular fibrous mass in place of the vitreous body. In addition, coloboma of the retina, rudimentary development of the iris and ciliary body were found. Many of these animals also have internal defects. The lungs and the pleural cavities are underdeveloped and the heart muscle is spongy. Diaphragmatic hernias are frequent. The renal pelvis and the ureters are not dilated as in normal young, which indicates that the kidneys do not function. Their lower poles may be fused and horseshoe kidneys formed. Undescended testes are seen and many anomalies of the urogenital duct system can be demonstrated.

One may ask whether these young show the cardinal sign of vitamin A deficiency, namely, the appearance of keratinized epithelium in places where such epithelium is not ordinarily found. An interesting phenomenon was discovered in our animals by Dr. James Wilson of Rochester who found stratified keratinized epithelium in structures derived from the urogenital sinus (9). Such keratinized epithelium was not found in fetuses under 18 days gestational age. That is the time when keratinization of the skin begins in rat fetuses. Before this time the fetus has probably not the ability to form keratinized epithelium. The young fetus responds to vitamin A deficiency by formation of morphologic anomalies and not before the end of the fetal period do we see the beginning of a reactivity comparable to that of the postnatal period. We should remember this fact and not expect that the tissues of embryos and fetuses respond to nutritional deficiencies like those of small adults. They have their own metabolism, their

debility of the young has been observed as a result of absence or reduction of any of these substances in the maternal diet. It must be stated, however, that some investigators reported successful reproduction in spite of maternal deficiencies of the same nutritional elements. Such divergent reports are not necessarily contradictory. The differences in the results are accounted for by the variance of the duration and intensity of the dietary restrictions. There were also differences in the species employed and in the examination of the young. The experiments are, as a rule, in better agreement than the interpretations and generalizations derived from them.

It is obvious that the type of nutritional element in which the mother is deficient plays a role in the outcome of pregnancy. Some substances are tenaciously held in store, others are readily released; some are obligatory and others can be synthesized within the mammalian organism.

The most interesting results are obtained in experiments in which a borderline deficiency exists in the maternal diet. It was found by *Macomber* that in the

TABLE I

Protein	Calcium	Vitamin A
Fat	Phosphorus	Thiamin
	Sodium	Riboflavin
	Potassium	Vitamin C
	Manganese	Vitamin E
	Copper	Vitamin K
	Iodine	
	Iron	

rat pregnancy can be terminated successfully although the maternal diet is low in calcium. This, however does not mean that an adequate calcium supply is unnecessary for optimal reproduction. *Sherman and Campbell* showed that a diet adequate in the sense that it maintained normal growth and successful reproduction could be improved by an increase of its calcium content. The females on an increased calcium intake showed a longer period of ability to reproduce, bore more young and reared a higher percentage of them.

Maternal borderline deficiencies afford us an insight into the struggle between mother and offspring for the necessary nutritional factors.

Let us first consider the contest between mother and fetus for vitamin C. It seems that in regard to this substance the fetus is actually capable of behaving like a parasite. *Teel* (3) and coworkers state that the fetus draws vitamin C from the mother as long as appreciable amounts of ascorbic acid are present in the maternal plasma. And several studies, especially those of *Manahan and Eastman*, have shown that the vitamin C content of the blood plasma of the fetus is higher than that of the mother (4).

The situation is different in regard to vitamin A. If the mother's intake is low, the intrauterine development of the offspring may be endangered although

Maternal nutrition is only *one* factor which influences human reproduction and we are not justified in making it responsible for all forms of failure. The fact that a malformation can be produced under certain conditions in rats by a dietary deficiency of the mother does not mean, of course, that this malformation is always caused by maternal nutritional deficiency. Cleft palate may be genetically determined in one case, caused by maternal riboflavin deficiency of the mother in another case and by x-ray irradiation of the mother during preg-
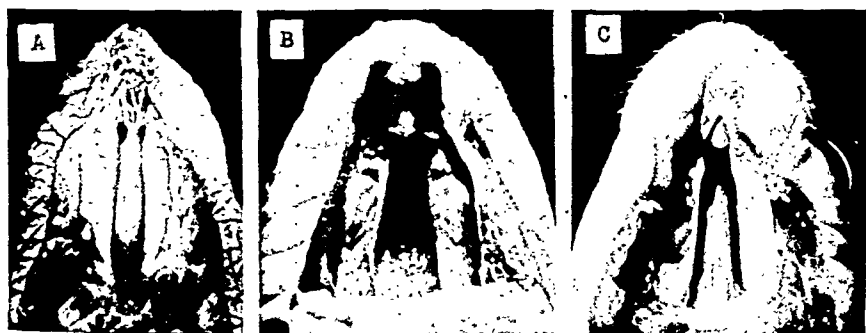
FIG. 1. Cleft palates of different etiology. A, Mouse derived from strain in which harelip and cleft palate were hereditary (Steiniger, F.: Ztschr. f. menschl. Vererb.-u. Konstitutionslehre **23:** 427, 1939). B, Rat whose mother was deficient in riboflavin. C, Rat whose mother was exposed to roentgen rays on day 15 of gestation.
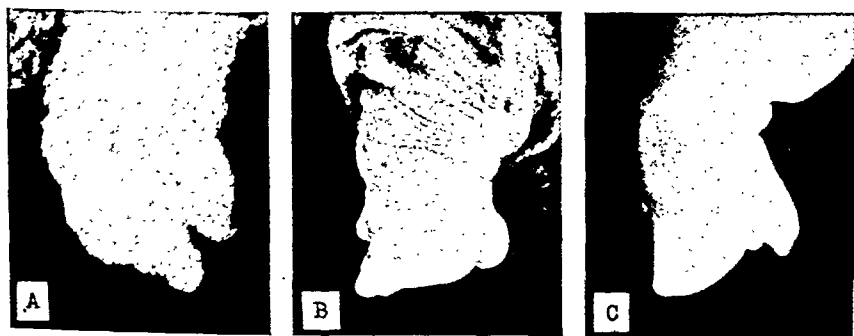
FIG. 2. Syndactylism of different etiology. A, Mouse derived from strain with hereditary congenital defects (Bagg, H. J.: Am. J. Anat. **43:** 167, 1929). B, Rat whose mother was deficient in riboflavin. C, Rat whose mother was exposed to roentgen rays on day 13 of gestation.

nancy in the third case (13). The same is true for other manifestations of reproductive failure like sterility, miscarriages and others. *The same results may be due to different causes* (Figures 1 and 2).

Animal experiments have shown that it is dangerous to make general positive statements about the relationship of maternal nutrition to reproductive failure. But it is equally dangerous to make sweeping negative statements in this field. I cite as an example the often repeated sentence that dietary deficiency of the mother leads either to intrauterine death or to the birth of normal young and

own requirements and their specific responses to adverse conditions which cannot be deduced from postnatal physiology and pathology.

Lack of nutritional elements has specific effects on morphogenesis. While prenatal vitamin A deficiency in rats results in congenital anomalies of soft tissues, it was found by Dr. Nelson, Miss Schraffenberger and myself (10, 11) that female rats bred on riboflavin deficient diets give birth to young with congenital skeletal malformations. Shortness of the mandible, tibia, fibula, radius and ulna, syndactylism, cleft palate, fusion of the ribs and centers of ossification of the sternum were observed in about one third of the young. None of the soft tissue changes seen in prenatal *vitamin A* deficiency was found. The size of the young was approximately normal at term. · On the riboflavin deficient diets employed the mothers did not thrive. Their weight was stationary and they developed alopecia, but many were well enough to give birth to several litters. In this case, a borderline deficiency of the mother had deleterious effects on the morphogenesis of the young. We do not have any proof that riboflavin plays an important role in the metabolism of bones in the postnatal period, but our experiments suggest that a high riboflavin level is needed in the *prenatal* period by the *membranous* skeleton which is the forerunner of the cartilaginous and osseous skeleton (11). Recently we have tried to breed a special strain of mice on a riboflavin deficient diet. The results were different from those obtained in rats. The young born at term were small and of subnormal weight but no skeletal malformations have been observed so far. Different species have different nutritional requirements, different ability to store or synthesize nutritional elements and different ability to breed under adverse circumstances. Nutritional requirements may even vary between several strains of the same species as shown by *Rodgers, McElroy and Cowgill* (14) who experimented with two inbred strains of mice and found that their dietary requirements for reproduction differ.

Ross, Philipps, Bohstedt and Cunha (12) observed syndactylism, talipes, kinked tail and blindness in pigs whose mothers were bred on a deficient diet consisting of yellow corn meal, soy bean oil meal, alfalfa meal, calcium carbonate and iodized salt. The preventive factor for these malformations has not yet been determined. A slight change in the maternal diet I results in different malformations of the young of rats. On a diet high in calcium, low in phosphorus, containing riboflavin, and lacking in vitamin D young are obtained which appear externally normal but show skeletal anomalies when they are cleared (9). Changes specific. No overlapping.

There are a few points we can learn from these animal experiments. We see that starvation and lack of certain essential nutritional elements can interfere with successful reproduction. Animal experiments afford an opportunity to analyze which reproductive function is impaired and they permit us an insight into reproductive failure.

Observations of animals demonstrate that different species react in different ways to nutritional deficiencies. We should not take it for granted, therefore, that the results obtained in animal experiments necessarily apply to human conditions.

between the fetal blood and the maternal blood in the animals and in some of them the fetus does not live on the dialysate of the plasma of the mother.

There is also a group specificity; certain anomalies occur in certain animals and will not occur in others.

I also understand that the weather has been associated with anomalies in the human. I do not know whether this occurs in animals.

Peterson of Chicago thought that there was some relation between the time of conception and the Spring Equinox in the development of fetal abnormalities.

Dr. Potter, our fetal pathologist, has given me the following data: heredity is still the important factor in the production of minor abnormalities (cleft palate, extra digits, etc.) in human fetuses. Major anomalies have an unknown etiology. Perhaps it is the weather. It is conceivable that it is diet, but it is going to be extremely difficult to prove. Major anomalies of the fetus have occurred in some of our nutrition patients who had excellent diets during pregnancy. Practically all malformations in the human are believed to be

TABLE A

Ascorbic acid content of plasma of maternal and cord blood taken at the time of delivery

VITAMIN C CONTENT OF MATERNAL DIET					
Normal or Above Plasma Ascorbic Acid, Mg. per 100 cc.		Suboptimal Plasma Ascorbic Acid, Mg. per 100 cc.		Deficient Plasma Ascorbic Acid, Mg. per 100 cc.	
Maternal Blood	Cord Blood	Maternal Blood	Cord Blood	Maternal Blood	Cord Blood
1.0	1.9	0.5	1.8	0.1	0.5
0.8	1.5	0.1	0.5	0.2	0.6
0.6	1.4	0.4	1.5	0.1	1.0
1.0	1.9	0.5	1.0	0.1	0.8
0.9	1.7	0.5	1.0	0.2	1.0
0.9	2.4	0.6	1.3	0.5	1.2
0.8	1.7	0.5	1.4	0.5	1.1
1.0	1.7	0.4	1.0	—	—
1.0	1.8	—	—	—	—
Average Values in Mg. per 100 cc.					
0.88	1.77	0.44	1.19	0.24	0.89

(Courtesy of the Am. J. Dis. Child. 56: 1004–1010, 1938.)

determined before the 8th week of embryonic life, at which time organogenesis is complete. Since the doctor and the dietitian rarely see the patient before or even during this period, it would seem as if diet after that time could have relatively little effect on the production of most malformations.

MRS. BERTHA S. BURKE: Dr. Warkany referred to a paper by Teel and co-workers which is an early publication from our group. You might be interested in Table A, as it illustrates "the contest between mother and fetus" to which Dr. Warkany referred.

The plasma ascorbic acid content of the maternal and cord blood taken at the time of delivery is shown. It is interesting to note, that when the maternal blood is relatively high in ascorbic acid the plasma value of the cord blood of the infant averages a little more than twice the plasma value of the mother's blood. However, when the ascorbic acid value of the mother's plasma was only 0.5 mg. per cent or less the ascorbic acid content of the cord blood of the baby was three, four, and in cases where the mother's plasma had a value of only 0.1 mg. per cent the infant's was five or more times that of the mother. This

that injury to the offspring or malformations cannot be produced by dietary restrictions of the mother. We have learned that the young of deficient mothers may appear externally normal but that does not mean that they *are* normal. By visualization of the skeleton or by histologic examination one may find anomalies which evade the superficial observer.

Thus animal experiments can be very helpful in the investigation of reproductive success and reproductive failure. They can direct investigators of human reproduction into certain channels and they can help us avoid erroneous deductions. But final conclusions concerning human reproduction can be drawn only from observations in man.

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DISCUSSION

DR. WILLIAM J. DIECKMANN: I do not think anyone doubts that these experiments which Dr. Warkany reports of his own and others occurred in these animals. He made it very clear however that it required an extremely deficient diet before the anomalies would occur. If the animals were on this diet before conception, conception would not occur. I doubt whether we will ever see this experiment repeated or carried out in the human. There is a tremendous difference in the placentation between animals and humans. The only placenta approaching the human is the one in the primates. There are many layers

tricians and of the embryologists interested in human defects is to find out which of the various kinds of causes that may produce defective embryos are operative most commonly and which has operated in any individual case.

No doubt Dr. Dieckmann is correct in his belief that such abnormalities as Dr. Warkany has produced in his rats through the use of defective diets will not often occur in the human embryo from the same causes. Such extreme limitations of diet are certainly rare in human communities. It is relatively certain, indeed, that no large proportion of human embryonic malformations can be ascribed to unsuitable maternal diets.

It would be very dangerous, however, to let ourselves take an obscurantist viewpoint, so that we might fail to recognize nutritional causes if they do result now and then in producing human embryonic abnormalities. It is probable that sooner or later disturbances of human embryonic development will be found to result, in various cases, from all the different kinds of possible causes which have been shown effective in experimental animals, that is to say from genetic disturbances and from environmental accidents due to trauma and to maternal humoral and nutritional disturbances.

CHAIRMAN EASTMAN: The importance of Dr. Warkany's contribution, as I see it, lies in the fact that it supports the general theme that environmental deficiencies may bring about defects in the conceptus. I do not believe that Dr. Warkany had in mind any such implication as Dr. Dieckmann pointed out. The likelihood of such dire dietary deficiencies in the human is extremely remote and I do not believe Dr. Warkany meant to suggest that defects in the human fetus are frequently due to this cause. Nevertheless, we do know in the human that environmental abnormalities of other types can produce defects. Witness rubella. We are faced then with the general problem as to how frequently a bad egg is the result of genetic factors and how frequently it is attributable to environmental deficiencies or abnormalities.

As an embryologist sits in his laboratory and studies abortuses, he will naturally find that a large number of them are defective. It seems to me that the implication in the past has been too much that these defective abortuses are usually genetic in character and that the bad product of conception was fore-ordained at the moment conception took place. Is the evidence not accumulating that many of the defective abortuses may be due to environmental lack of some kind or another, perhaps thyroid lack, perhaps other hormonal lack, perhaps dietary lack, etc.?

This is a most important clinical issue because we obstetricians obviously would have nothing to gain in attempting to treat abortion, or repeated abortion, if all these bad ova, which are so frequently present in abortion, were due to genetic factors.

Dr. Hertig, would you like to comment on that statement?

DR. ARTHUR T. HERTIG: The point which Dr. Eastman has raised is certainly a very pertinent one. I don't know that we have any data that answer his question. I can only cite again the relatively small series of abnormal ova that were destined to abort and which we found in surgically removed uteri prior to the first missed period. Many of you did not hear the paper on this subject that I gave before this conference last year. Briefly the data were these: 26 implanted ova were recovered from a series of known fertile patients in whom the previous pregnancies had terminated in approximately six normal, full-term babies. Of these 26 early pregnancies discovered before the first missed period 40 per cent were definitely abnormal; abnormal in various ways and to various degrees.

So far as we could tell there was absolutely nothing wrong with the reproductive efficiency of these particular 125 patients from which these 26 early ova were found, that is, their past reproductive histories were good. Whether or not they were on an adequate diet at the time these ova were found is a moot question because the pregnancies were incidental findings following hysterectomy. These uteri were removed for surgical conditions and we knew relatively little about the environmental background of the patients with respect either to infection, vitamins, endocrine deficiencies or dietary status. All we can say is that these particular patients did have a very good reproductive background in that they had produced a good many children and that the endometria on which these ova were found

illustrates that the fetus is parasitic apparently to a degree depending upon the mother's nutritional state.

The work of Wallace on sheep done under Barcroft in England is extremely interesting. When Wallace was returning to Australia, he visited our group in Boston and I had the privilege of seeing the illustrations in his thesis. In discussing his work he showed drawings of sections where the deficient mother appeared to give to the fetus protein from her body until a certain level was reached. Then as he expressed it, her depletion had reached a stage where she continued to give reluctantly and finally did not seem to be able to give any more and under these conditions the fetus suffered.

DR. S. W. KLETZIEN: In connection with the use of rachitogenic diets, I would like to call attention to the findings of Remington, who discovered that you could produce goiter in rats with rachitogenic diets.

Then I would like to recall the earlier work of Jacques Loeb of changing the inorganic salt concentration of water whereby he was able to produce malformations in marine life. I think it is a thing that many have forgotten.

Also there is the comparison that the late A. P. Collup made with reference to the similarity of relative concentration of inorganic materials which you have in salt water and the sera of different animals.

By my own work in this particular line I was able to show some fifteen years ago that a high calcium intake will decrease iron assimilation. Not only is that true of calcium but the other members of the alkaline earth metals have such effects. Contrary, it is not true of the alkali metals, so that you have interplay of alkali and alkaline earth metals which influences the assimilation of the minor inorganic elements.

I believe before we ascribe the development of these malformations to some one vitamin we have to be certain that the concentrations of our inorganic elements are normal.

DR. WILLIAM J. DARBY: It seems to me there are two mechanisms which should be mentioned here. The nutrition of the fetus depends, first, upon the nutrients in the mother's diet, and secondly, upon the nutrients which are passed on from the mother to the fetus. If by any chance a mother were well nourished and yet the process of transference of a nutrient to the fetus were defective, I should think that it would be possible for the fetus to experience a nutritional deficiency despite a perfectly well-nourished mother.

It is conceivable too, considering the nutritional levels at which these mother animals must exist in order to produce defective young and the clinical experience which we have had at Vanderbilt, that if fetal nutrition does play a role in the production of congenital malformations in the human, it may be through the indirect process rather than through the direct process. That is to say that the mechanism is defective transfer of nutrients, not a grossly deficient maternal diet.

DR. GEORGE W. CORNER: I should like to re-emphasize one point which is very clearly brought out by Dr. Warkany's work. That is that he, like previous experimenters, has shown that embryonic defects of exactly similar type may be produced either by genetic factors or by environmental injuries caused by physical trauma, by x-ray, by chemical injury or, as in this case, by nutritional defects.

It seemed very strange that such dissimilar causes could produce similar defects, until the situation was considered in the light of what the experimental embryologists have been teaching us about the way in which the embryonic body is organized. The so-called theory of organizers shows us that the development of a normal individual is the result of a chain of events within the embryo. Each developing tissue acts to organize the undifferentiated tissue adjacent to it into new tissues and organs. Thus each step in the development of the body depends upon the completion of a previous step. The chain of events may be interrupted or delayed at any time. No matter whether the harmful agent is a toxin or physical injury or on the other hand the effect of a gene or of some constitutional accident, its interruption of the chain of organization at any given time will produce the same kind of defect. Although the experimental evidence has necessarily been obtained from lower animals, the theory certainly applies to the human species as well. The problem of the obste-

In our experiments, we have not imitated human diets, and we were not interested so much in the practical questions involved. We were interested in proving that an environmental factor could induce anomalies. At the time when we began our experiments there were many who said this was impossible in higher animals. Of course, thanks to the work of Stockard and others, the possibility was conceded in lower animals.

Now there is no difference of opinion with geneticists. The term "phenocopy" was made by geneticists, and Dr. Goldsmith calls a "phenocopy" a morphologic character—normal or abnormal—which imitates a hereditary trait, although it is caused by environmental factors. In our case (Fig. 1) the cleft palate on the left is hereditary; the others are phenocopies, non-hereditary imitations produced by interference with normal development. Dr. Corner has discussed this point already and I do not have to repeat it.

I think we have to learn to look at congenital malformations as symptoms of prenatal pathology, and as we know, symptoms may have different causes. A cough may be caused by tuberculosis but it may be caused by many other diseases. If in 20 per cent of the cases "cough" is caused by tuberculosis we should not say all coughs are "tuberculous." The same is true for cleft palate and syndactylism.

I should not discuss "bad eggs" since I am not an embryologist and I may get in trouble here; but I have seen eggs and I have eaten eggs. It seems to me that not all in an egg is germ plasm. Is that correct?

DR. CORNER: Right.

DR. WARKANY: So I think a "bad egg" may show faulty development not because of anomalies of the germ plasma but because of defects in the cytoplasm—which is part of the "environment."

were perfectly normal by any ordinary histological criteria.   These data cannot answer Dr. Eastman's pertinent question any further but it would seem that those intrinsically defective ova were certainly destined to abort and that the environmental factor, if any, was of a very obscure nature.

I think Dr. Corner can comment on this question better than I as to whether he thinks that these ten defective ova were perhaps on a genetic basis or whether they were due to environmental or other factors.

DR. CORNER: I shall be very glad to.   I know there has been a good deal of question in the minds of persons not intimately familiar with early human embryology, who have seen these pictures of embryos presented by Dr. Hertig, as to how badly defective they really are. Some of the lesions which have been shown may seem at first sight rather trivial.   It is quite relevant to the present discussion to inquire whether these embryos would have died in utero or if they had lived would have been defective at birth.

I can only say that the original specimens have been thoroughly studied not only by Dr. Hertig but by my distinguished predecessor in the directorship of the Carnegie Embryological Laboratory, Dr. George L. Streeter, and by my colleague Dr. Chester H. Heuser.   These two men, who no doubt are more expertly familiar than anyone else with the earliest stages of human embryology, are convinced that these are all examples of genuine and serious early human embryonic defects.   From my own not inconsiderable experience with very early embryos of other species, I am in agreement with this thought.   All the cases shown by Dr. Hertig today occurred very early and, as he says, we have no reason to think that the environmental conditions existing in these women were detrimental to the embryos.   As far as his evidence goes, it indicates strongly that a large proportion of the anomalies of human embryos are produced by causes which we must classify under the term "genetic," that is to say constitutional effects depending upon the chromosomes.

I think I had, through my work of years ago on early abnormal pig embryos, as much as anybody to do with spreading the notion among American biologists that defective mammalian embryos are largely produced by genetic causes.   In recent years I have reopened my experimentation and meanwhile have seen the evidence for production of embryonic defects in mammals by nutritional causes and by other environmental disturbances, such as that which occurs in German measles.   It now seems to me highly probable that some defective human embryos are the result of genetic factors and others of unfavorable maternal environment.   The task now before us is to get quantitative knowledge as to the proportionate influence of genetic and environmental factors respectively.   Since both causes are known to operate in experimental animals, both no doubt are operative in humans.

CHAIRMAN EASTMAN: It is very gratifying to have an embryologist concede that a certain proportion of defective ova are due to environmental conditions.   Following the history of that teaching, from Dr. Mall on to Dr. Streeter, they have all emphasized the genetic side of the picture and they may be quite right; but both yesterday and today the question has been raised again as to the role of environment.   It was appropriate I thought that it be dwelt upon for a few minutes on this occasion.

DR. WARKANY: Most of the questions have been answered much better by the discussants than I can do.

I agree with Dr. Dieckmann completely in that we are talking about animals while he is talking about children and we should be very careful not to confuse the two observations.

On the other hand, I think one should also be careful with negative statements, and that has been brought out by Dr. Corner.   One cannot say, for instance, that cleft palate in the human is always hereditary.   I have reviewed this chapter.   Most of the observers who take histories in families in which cleft palate occurs find in only 20 per cent a second case in the same family.   There is one study, I think, in which in 40 per cent of the cases, two or more members in a family were affected, but that was in a certain area where apparently an abnormal gene was prevalent which may have caused a higher incidence through inbreeding. In a region where there is no defective gene one may find non-hereditary causes more prevalent.

Biochemical measures are available for but a small portion of the forty or more nutritional essentials. It is naive to expect an evaluation of so few factors to give one information relative to the total group of important dietary constituents. If properly chosen, however, available technics may provide a quantitative index to the consumption of certain types of foods.

Measurements of blood concentrations are possible for several vitamins—A, E, riboflavin, thiamine, niacin derivatives, C, and K (indirectly by prothrombin estimation). Dependable macro- and micro-technics are available for most of these and the same measurements may be carried out by either procedure. Most of the data in the literature were obtained by use of macro-technics. Macro methods require venous blood samples, but have the advantage of demanding less highly trained personnel and less special equipment. The microprocedures permit use of finger tip blood and are preferred by some investigators. The choice between reliable technics to be employed for nutritional work should be made with due consideration of available personnel and equipment, not upon the basis of the method which is "in vogue" at the moment. Data obtained by both types of procedures are subject to similar limitations of interpretation.

It is the aim here to discuss in general some of the problems posed by efforts to interpret biochemical findings and to illustrate some of these points by preliminary data from a study which is in progress at Vanderbilt University Hospital. This study has been continuous since September, 1945, and is known as the Vanderbilt Cooperative Study of Maternal and Infant Nutrition. It is a cooperative project of the Departments of Obstetrics and Gynecology, Pediatrics, Preventive Medicine and Public Health, Biochemistry, and Medicine. This study is devised so that the nutritional level of each woman in the Vanderbilt University Hospital ante-natal clinic is determined. The methods of study include a 7-day dietary record, laboratory examinations of body fluids, and physical examinations. Each of these is repeated once per trimester and on the 6-week post-partum visit. No routine supplementation of diet or intensive dietary instruction is carried out, so that the women are to be considered as on self-selected diets. To date over 1700 women have entered this study, 1300 of whom have delivered. The sample is not heavily weighted by complicated pregnancies as indicated by a pre-eclampsia[2] rate of 5% and a puerperal morbidity[3] rate of 6.1%.

The laboratory studies which are made consist of:

Hemoglobin
Erythrocyte count
Packed cell volume

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[2] Pre-eclampsia (non-convulsive toxemia)—diagnosis is made with any two of the following: 1. A systolic blood pressure of 140 mm. Hg. or more for two days or longer. 2. Edema of no obvious etiology involving at least the ankles and legs. 3. Proteinuria which is present for two days or more.

[3] Temperature of 100[4] for two successive days, excluding the first 24 hours post-partum, during the hospital stay of the patient. Oral temperature recorded 4 times daily.

THE BIOCHEMICAL ASSESSMENT OF NUTRITIONAL STATUS DURING PREGNANCY[1]

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The subject of nutrition in pregnancy has been reviewed so ably of recent date (Garry and Wood, 1945–1946; *Proc. Nut. Soc.*, 1944; Dieckmann and Turner, 1945) that no attempt will be made in this report to cover the vast literature. It is apparent, however, that some investigations have yielded remarkable correlations between the nutrition of the mother and her course during pregnancy and the condition of the offspring (Ebbs, Tisdall and Scott, 1941; Burke, Beal, Kirkwood, and Stuart, 1943; People's League of Health, 1942; Leverton and McMillan, 1946) while other workers have observed little correlation between these attributes (Williams and Fralin, 1942; Dieckmann *et al.*, 1944; Smith, 1947; Sontag and Wines, 1947). Most such studies have relied entirely upon the dietary history as a measure of nutritional state or have dealt with the effects of empirical supplementation. It is imperative that more quantitative evaluations of nutritional state be obtained in order to answer the important question of whether the nutritional level of the mother is related to her course during pregnancy and, if so, in what nutritional zone the correlation becomes evident.

Biochemical assessments of nutritional level would appear to offer means of studying this question. They, too, however, suffer from the disadvantage that interpretation of chemical assessments are subject to disagreement among nutrition workers themselves (Dann and Darby, 1945; Stare, Hegsted, and McKibbin, 1945; McHenry and Leeson, 1947; Darby, 1947). Many investigators trained primarily in the field of nutrition have failed to acquaint themselves with the several excellent studies of nutritional factors in pregnancy which have been reported by obstetricians. The latter, in turn, have not always been alert to the influences which alter laboratory findings in non-pregnant individuals, and to the limitation of the interpretation which can be placed upon biochemical assessments.

A most striking finding is that the lowest concentrations occurred at the post-partum examination and only during the season of highest intake did this mean approach that of the ante-natal examinations. This is in agreement with Robinson and Kaser's (1944) observation that lactating women in Williamson County, Tennessee had the lowest serum levels of any age-sex group of the population. Anderson and his co-workers (1946) noted the same post-natal decrease in Mexico City.

MEAN SERUM ASCORBIC ACID BY MONTH
AND TRIMESTER OF PREGNANCY

NUMBER OF DETERMINATIONS

	J-F	M-A	M-J	J-A	S-O	N-D
I.	17	19	24	9	23	10
II.	66	66	79	50	115	65
III.	167	92	125	51	140	141
P.P.	83	71	83	40	72	75

TOTAL DETERMINATIONS 1683
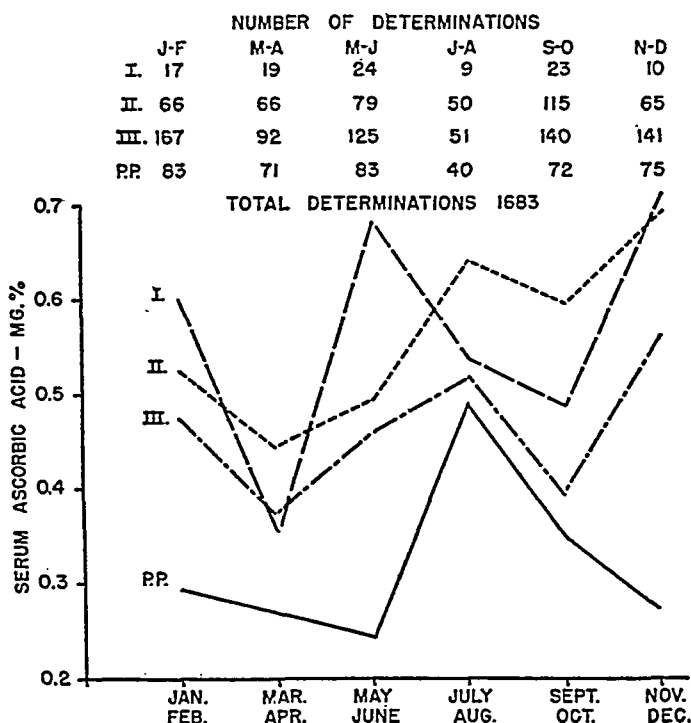
FIG. 1. Mean serum ascorbic acid by calendar month and trimester of pregnancy. Note the seasonal variations which occur in all groups despite the separation of values for each period of pregnancy. The less consistent behavior of the values for the first trimester (I) is probably due to the smaller number of determinations.

Whether these low values in the puerperium are correlated with lactation is of interest. We have previously reported a preliminary tabulation indicating that the concentration is lower in women who were lactating than in the comparable non-lactating post-partum group (Kaser and co-workers, 1947). This is of interest in view of Doctor Hoobler's finding (1947) that some women with very low blood concentrations of ascorbic acid are nevertheless excreting 40 to 60 mg. of vitamin C per day in breast milk. Doctor Hoobler (1947) has

Serum vitamin A and carotene
Serum ascorbic acid
Serum protein and albumin
Plasma total tocopherols
Urinary excretion of
   Thiamine
   Riboflavin
   N'-methylnicotinamide
Radioactive iron uptake

Most of these biochemical measurements have been studied during pregnancy by other workers, but only one group (Anderson *et al.*, 1946) has reported composite data on several of them on the same individuals. This report did not correlate the findings with clinical results and did not extend the data over such a period of time as we are doing.

The illustrative data discussed here are offered as tentative tabulations only. They are preliminary in nature and represent but a small portion of our accumulated data. We shall avoid interpreting them in terms of health at this time. They are presented merely to emphasize some of the factors which must be considered as one attempts to analyze biochemical findings related to nutritional status.

Vitamin C. Serum or plasma concentrations of ascorbic acid are more rapidly altered by changes in the dietary intake than are the levels of most other dietary factors. The mean plasma level of homogenous groups, therefore, gives an indication of the abundance or lack of recent vitamin C intake. Considered alone, low plasma values do not necessarily signify deficiency changes in the tissues (Crandon, Lund, and Dill, 1940; Farmer, 1944). Not infrequently one encounters patients with no measurable quantities of ascorbic acid in the serum, but this does not necessarily mean that such persons have scurvy.

The trends of our findings on this vitamin are illustrated by Fig. 1 in which the mean serum ascorbic acid concentration during different calendar months is represented. The data from the 3 trimesters of pregnancy and the 6-weeks post-partum examination are shown separately. It is to be noted that the number of persons included for the first trimester was smaller. This may account in part for the greater variations in this period. However, the data exhibit the expected seasonal trends reflecting seasonal intake regardless of the time in pregnancy. Peaks are seen in the summer and fall seasons and lowest points appeared in winter and early spring. Similar seasonal fluctuations have been observed within the general population of this and like regions in the South (Milam, 1942; Manning and Milam, 1943; Darby and Milam, unpublished) and among pregnant women in Wisconsin (Lund and Kimble, 1943). In Great Britain (Craig, Lewis, and Woodman, 1944) saturation tests have revealed greater reserves of ascorbic acid in pregnant women from June to October.

Irrespective of the season, however, there is a slight downward trend during successive periods in the serum concentrations of the vitamin in these women on self-selected dietaries—an observation frequently made by others (Teel, Burke, and Draper, 1938; Anderson and co-workers, 1946).

reported that a rise in tocopherol levels occurs in the latter part of pregnancy—from a mean value of 1.17 ± 0.19 mg. per cent in the first 24 weeks (11 subjects) to 1.62 ± 0.31 mg. per cent between the 25th to 36th week (12 subjects).   They further reported a maternal blood: cord blood ratio of 5.7.   Our data confirm this increase in lipid soluble vitamin E.   The mean values for successive trimesters are 0.84 ± 0.03; 1.07 ± 0.01, and 1.24 ± 0.01 and at the 6-week post-

MEAN SERUM VITAMIN A AND CAROTENE
BY TRIMESTER OF PREGNANCY
1945—1947
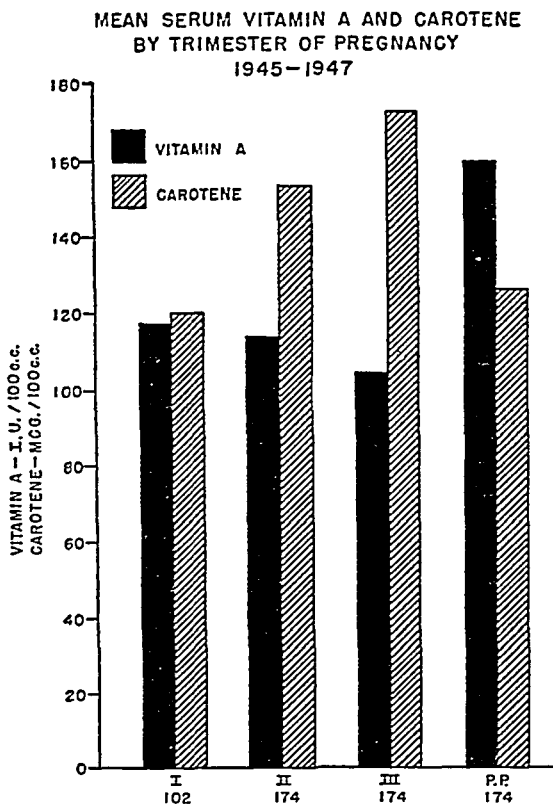
FIG. 2. Mean serum vitamin A and carotene by trimester of pregnancy.   The four pairs of bars are for the first, second, and third trimester and post-partum period respectively. The numbers at the bottom are the number of subjects included in each period.   The same individuals recur in successive periods.

partum examination 0.96 ± 0.04 mg. per 100 c.c.   We have observed concentrations as low as 0.5 mg., but it is to be emphasized that without further analysis of the data one cannot interpret the significance of such findings.

The B-vitamins.   The urinary excretion of a water-soluble vitamin or its metabolite is widely employed in efforts to evaluate nutrition.   The test may be made on a fasting specimen, on a total 24-hour collection, or on a timed sample collected after a standard oral or parenteral test dose.   These various technics give somewhat different results but are usually assumed to reflect recent dietary

further noted that there is an increased urinary loss of ascorbic acid the first few days following parturition.

Vitamin A and Carotene. Vitamin A levels in the serum are not rapidly altered by deficient intakes (Vitamin A Sub-committee, 1945) but are known to be depressed by several metabolic processes, especially in hepatic diseases (Haig and Patek, 1942; Adlersberg, Sabotka, and Bogatin, 1945; Harris and Moore, 1947). Carotene levels, however, are more labile and fall more rapidly when the intake of the pigment(s) is curtailed. Carotene levels tend to reflect dietary intake (Hoch, 1943), but again may be altered by disease. Thus, they are often abnormally high in hepatic disease, in xanthomatosis, etc., and low in disturbances of fat absorption. Hence, alterations in levels may be related to dietary intake, absorptive capacity, storage, rate of release of the vitamin from storage, or perhaps blood lipid concentration. Clinical signs of avitaminosis A, such as nyctalopia or xerophthalmia, are associated with blood concentrations of 0–40 I.U. per 100 c.c. (Hsu, 1943; Van Veen and Postmus, 1947; Vitamin A Sub-committee, 1945).

The mean serum vitamin A concentrations in our studies reflect to some extent the seasonal intake—the peak of the levels are obtained in the summer. In common with numerous other investigators (Bodansky, Lewis, and Lillienfeld, 1943; Lund and Kimble, 1943; Anderson and co-workers, 1946) our subjects have exhibited a decrease in serum A from the second to third trimester. The mean post-partum values, however, are considerably higher at all seasons than are those during pregnancy. Lund and Kimble (1943) found that a rise in vitamin A concentration occurs within 48 hours following delivery. It is difficult, therefore, to escape suggesting that these various changes are in part of metabolic origin.

Serum carotene levels show two separate seasonal peaks—coincident with availability of spring and fall fruits and vegetables. In addition to the seasonal variations, there are distinct increments from trimester to trimester with the highest mean value occurring in the latter 3 months of pregnancy. This is in confirmation of Bodansky, Lewis and Lillienfeld (1943) and Anderson and co-workers (1946). The post-natal decrease in carotene has also been reported by Anderson *et al.* (*loc. cit.*) from Mexico City. The inverse relationships here observed between carotene and vitamin A are illustrated more strikingly by the bar graph (Fig. 2). Obviously, for an interpretation of the obstetric significance of blood levels it is imperative that sufficiently large groups of women be studied to permit proper consideration of changes associated with season as well as metabolic changes peculiar to pregnancy.

Vitamin E (Tocopherols). Variations in vitamin E levels in health or disease are not as yet clearly defined. Inasmuch as tocopherols are fat-soluble and are not excreted in the urine (Hines and Mattill, 1943) one might expect the concentrations of E to resemble somewhat vitamin A or carotene in their behavior. At least under conditions of altered fat absorption the changes in the blood level of vitamin E and carotene do behave similarly (Darby, Cherrington, and Ruffin, 1946; Darby, Jones and Kaser, 1947). Straumfjord and Quaife (1946) have

tions occur in the winter and early spring months. This corresponds to the season of high pork and dried legume intake in our area, so is perhaps to be expected on the basis of dietary consumption. There is a stepwise fall in the average thiamine excretion from trimester to trimester with something of a rise in the post-partum above that of the last quarter. Siddall and Mull (1945) observed similar decreases in the 24-hour output of thiamine in the latter stages of pregnancy, and Lockhart, Kirkwood, and Harris (1943) found that more thiamine was required late in pregnancy to produce a given urinary excretion peak than was necessary early.

Riboflavin excretions showed no significant variation from trimester to trimester, but they were significantly lower at the post-partum examination.

N'-methylnicotinamide excretion following a test dose of nicotinamide is greatly increased as one passes from a given period of pregnancy to the next. By the time of the six-week post-natal examination, however, the value has returned to a pre-pregnant average. An attempted explanation of these findings would only be hypothetical at this time, but it is obvious that these results are not merely reflecting dietary variations. Certainly one must be cautious in interpreting laboratory findings *per se* as evidences for or against deficiency states.

One may raise the questions "Does the fall in plasma concentration of various nutrients during pregnancy merely reflect a dilution of the circulating nutrient?" and "Is the increase in fat-soluble substances in the plasma only a reflection of the lipemia which is known to occur?" Evidence bearing on these points may be obtained by comparing the percentage dilution due to plasma volume change (Dieckmann and Wegner, 1934) with the decrease in concentration observed for several of these materials (Fig. 3). It would appear that the magnitude of the decrease of vitamin C, hemoglobin, and vitamin A is roughly of the order of such dilution but the total serum protein decreases less than expected by such reasoning. On the other hand, the observed percentage increases in carotene and tocopherol are considerably greater than the percentage rise in cholesterol or total lipids (Tyler and Underhill, 1925); hence, the rise in these fat-soluble factors must be something more than a reflection of lipemia.

<div align="center">SUMMARY</div>

We have attempted to point out that biochemical measurements which are applicable to studies of the large groups which are required to demonstrate the presence or absence of correlations between nutritional status and health in pregnancy permit objective quantitation of individuals. In our opinion they afford better quantitation than do other methods.

These measures are influenced, at times predominantly, by non-nutritional factors—metabolic changes—as well as by seasonal differences in dietary intake.

These influences are at work whether one has obtained the data by macro or micro-technics or by load tests.

Interpretation of biochemical data will remain insecure until many of these metabolic influences are clarified.

The present state of knowledge of the biochemical assessment of nutritional

intake—i.e. low excretion by any of the tests would usually be interpreted as indicating a low intake and a low state of tissue saturation. The verbs "assumed" and "interpreted" are employed here advisedly. These measures have been seized upon too readily by some enthusiastic workers without benefit of adequate testing of the validity of their assumptions. Nevertheless the tests
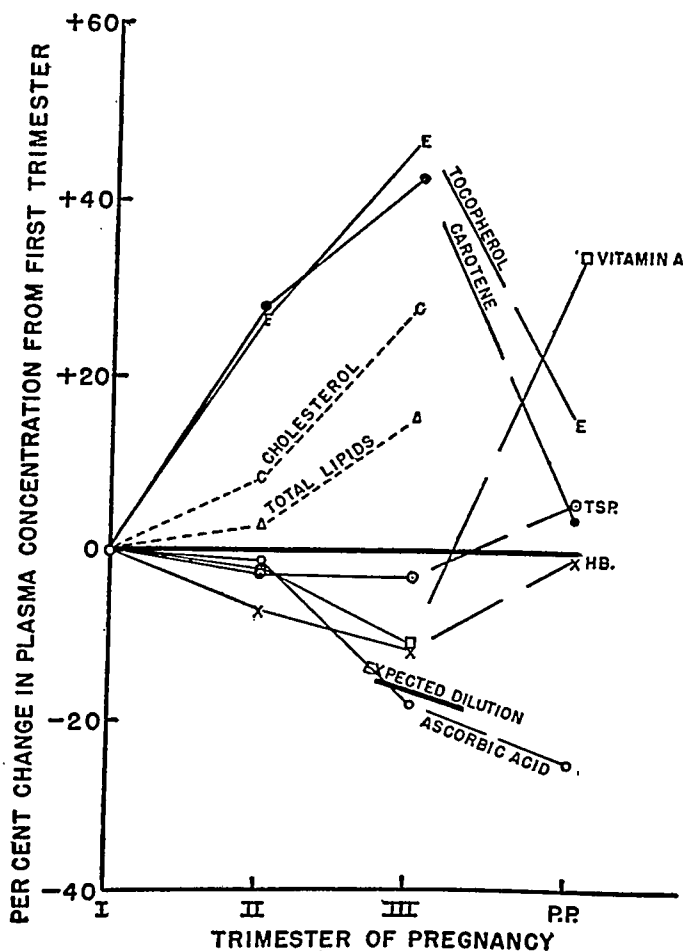
Fig. 3. Percentage change in blood concentration of several constituents. The "expected dilution" was calculated from the data of Dieckmann and Wegner (1934); the cholesterol and lipid values are from Tyler and Underhill (1925).

do indicate group differences if wisely applied. The significance for health of these variations remains to be defined.

We have adopted the expedient of collecting a two-hour urine sample following an oral test dose of 5 mg. of thiamine, 5 mg. of riboflavin, and 50 mg. of nicotinamide. We do not know of other applications of this identical technic to pregnancy studies. Our preliminary findings can be summarized as follows:

Thiamine. Again seasonal trends are observed—the highest average excre-

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DISCUSSION

DR. NEVIN S. SCRIMSHAW: I am going to bring up a slightly different aspect of the problem. Dr. Darby's very excellent description of the nutritional changes in normal pregnancy provides a very firm basis for the study of the influence of nutrition in abnormal pregnancy, yet many factors influence the incidence of complications of pregnancy and these factors can seriously confuse the interpretation of nutrition data.

I would like to describe the operation of one such factor which changed the interpretation of a study designed to determine the influence of nutrition on complications of pregnancy.

The unique payroll system of the Panama Canal divides all of the employees into a high income and a lower income group without any intermediate group whatsoever. There are three main racial groups: the Americans, the Panamanians and the West Indian Negroes.

level during pregnancy and lactation is one of *investigation, not of interpretation,* of observed changes.

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for a considerable period of time may lead to considerable confusion. That probably explains why different levels in blood concentration were given by the principal speaker.

DR. RICHARD CANNON: (Nashville, Tenn.) The composition of the group of patients comprising our cooperative study in the Vanderbilt Hospital Clinic is as follows:

Economically it is about a low middle class group and relatively homogenous. About 10 per cent of the patients are free cases in which no charge is made for the prenatal care or delivery. About 45 per cent pay an average of approximately $55.00 for one week's hospitalization at the time of delivery and about 45 per cent average some $30.00–$35.00 for the one week period.

At the present time 18 per cent of the patients are first seen during the first trimester, 45 per cent during the second and 37 per cent during the third trimester. We also have now 85 cases who have entered the study for the second time.

I would like to emphasize that we are studying all patients who enter our prenatal Out Patient Clinic at Vanderbilt Hospital, and not one patient is being eliminated in any way from the study.

DR. DARBY: I am not certain that I can add anything further except to agree with the points which have been made.

As Dr. Scrimshaw talked, it occurred to me that it might be well to point out that if one is studying a complication which alters plasma volume relationships, the only fair way to determine whether a given concentration change was related to the nutritional status before the complication was evident is to go back before there was any clinical evidence of this particular complication of pregnancy. For instance, if one had three determinations on every individual, two intermediate and one low, and this low one coincided with the time the patient was in trouble, the analysis should be based upon the finding prior to the development of the complication. Only by such a method can one know the nutritional background of the disease. For example, if hepatitis has developed, it is well known that the serum vitamin A will be low and the carotene high. The average of data on a group of subjects with hepatitis could lead to the false conclusion that faulty vitamin A nutrition was the determining factor in the development of hepatitis.

Certainly Dr. Pommerenke's point is important—we must know the nutritional level of these persons for a long time back.

It has been conservatively estimated by one of the English investigators that a rat can store enough vitamin A in the liver to live a hundred years. The human likewise has a large storage capacity. Hence, I think that when one finds rapid fluctuations downward of vitamin A levels in a group of people, either those persons are precipitously near a vitamin A deficiency, or else they have some metabolic disturbance which is bringing their vitamin A levels down. Conclusions can be valid only when it is possible to distinguish between the two causes of decreased concentration.

All of the West Indian Negroes and the majority of the Panamanians are in the low income group. All of the Americans are in a much higher income group, along with a minority of privileged Panamanians.

As would be expected, careful diet interviews showed that the high income groups had generally good diets and the low income groups had much poorer diets. Here then, with no intermediate group to confuse the results, seemed to be an ideal situation for determining something of the influence of nutrition on the incidence of abnormal pregnancy. With this background, we investigated the incidence of complications of pregnancy in more than 10,-000 Canal Zone and Panama women and found, to our surprise, that the incidence of eclampsia, pre-eclampsia, albuminuria and hypertension was essentially the same in the high income and low income Panamanians, i.e. in the good diet and the poor diet groups. There was no significant difference in diet between the Americans and the "Gold" Panamanians, and there was no significant difference in incidence of complications. But when it came to the West Indian Negroes, who had the same diet as the low income Panamanians, a very much higher incidence of the complications discussed was found.

Since differences in diet between the low income Panamanians and low income Negro group were not found, diet could not be operating to produce this difference in incidence of complications in pregnancy. Similarly, racial factors did not appear to be operating. In New Orleans, in American Whites and Negroes attending the same clinics as reported both by Arnell and by Levy, the incidence of eclampsia and pre-eclampsia is the same. If there were strong racial tendency in the Negroes to more pre-eclampsia and eclampsia, it should turn up in such a situation.

What then was the factor or factors responsible for the higher incidence in the Negroes? The Negroes in the Canal Zone are underprivileged. They also face discrimination, both from Americans and from the Panamanians. They usually are denied Panamanian or American citizenship. If they object to conditions in the Canal Zone, many can be sent back to the islands from which they came. No matter what skills or experience they acquire, they cannot escape this low income classification, and it is apparent even to the casual observer that many of them tend to be somewhat sullen and hostile. Except for racial background, the Negro group differed from the low income Panamanians only in their cultural pattern and environment.

We were forced to the conclusion, as discussed in the September 1946 American Journal of Obstetrics and Gynecology, that in this case social and psychological factors were influencing the incidence, not only of essential hypertension, which has been pointed out many times before, but also of eclampsia, pre-eclampsia, and of albuminura. This does not mean that nutritional factors are not important in pre-eclampsia. It means only that in the particular situation described nutrition was apparently not poor enough to produce an effect. Therefore, in the unique situation found in the Canal Zone, the importance of a factor other than nutrition could be demonstrated.

In summary, it can be recognized from the data mentioned that the relative importance of nutrition will vary in different studies, and that in the interpretation of nutrition data the influence of factors other than nutritional ones must be very carefully considered. I should like to add that despite the many difficulties of a mass quantitative biochemical study, such as Dr. Darby's, it offers a fundamental, very important and very necessary approach to the understanding of the role of nutrition in pregnancy.

Dr. Wesley T. Pommerenke (Rochester): I would like to mention that some of the difficulties which are encountered in the estimation of the blood levels of these various ingredients might be referable to the fact that one has to take into consideration the basic levels or reserves in the body.

I know it is rather jeopardous to interpolate data from species to species, but we might invoke certain truths learned from animals. You may take a bitch, or any such animal, and you can remove from such an animal weighing 15 kg., 200 cc. blood every day for about 10 days, replacing only the washed cells before a base line of plasma protein is reached. Any data that do not take into consideration the reserves and the pre-existing levels of intake

decrease in the woman's activity. In the prenatal study which was carried out by the Department of Maternal and Child Health of the Harvard School of Public Health, in cooperation with the Boston Lying-in Hospital, the average weight gain during pregnancy was approximately 24 lbs. This and other studies in relation to weight gain during pregnancy imply that a woman should be allowed to gain 20 to 25 lbs. above her ideal non-pregnant weight for height, age and build. Unpublished data from our study indicate clearly that if an underweight woman gains during pregnancy only as much as a normal or overweight woman she tends to give birth to a smaller infant, her own body showing a net gain at the expense of her fetus. Conversely, if an overweight woman restricts her calories sufficiently, she experiences a net loss in weight herself, but her infant tends to be heavier than average. These data indicate that the fetus may be parasitic upon the mother to a degree depending upon the mother's nutritional status when she enters pregnancy as well as upon the quality and quantity

TABLE I

Recommended daily nutritional allowances, normal woman, pregnancy and lactation

(Food and Nutrition Board, National Research Council)

NUTRITIONAL ESSENTIALS	NORMAL	PREGNANCY (4th THROUGH 9th MONTH)	LACTATION
Calories*	2100	2500	3000
Protein (Gm.)	60	85	100
Calcium (Gm.)	0.8	1.5	2.0
Iron (Mg.)	12	15	15
Vitamin A, I.U.†	5000	6000	8000
Ascorbic Acid (Mg.)	70	100	150
Thiamine (Mg.)	1.1	1.8	2.0
Riboflavin (Mg.)	1.5	2.5	3.0
Nicotinic Acid (Mg.)	11	18	20
Vitamin D, I.U.		400–800	400–800

* Energy requirements vary with activity, size of the person, etc.

† The requirement for vitamin A may be less if provided as vitamin A and may be more if chiefly in the form of carotene.

of her diet during pregnancy. From the clinical standpoint of the problem of weight gain in the pregnant woman it would appear that as much special consideration should be given the underweight woman to see that she gains properly as is now accorded the very obese pregnant woman in an attempt to restrict her weight gain. In either case, as in the case of the woman of normal preconceptional weight, it takes approximately 2000 calories of very carefully selected food to carry the recommended amounts of protein, minerals and vitamins.

The increased allowances recommended for protein and minerals given in the table are based upon the results of balance studies carried out by Macy, Dieckmann and others (5, 6). Undoubtedly pregnancy increases the need for all the vitamins but exact knowledge of these requirements is limited, and the vitamin values recommended for the latter part of pregnancy are largely empiric.

Since 1940 there have appeared in the literature studies on relatively large

NUTRITIONAL NEEDS IN PREGNANCY IN RELATION TO NUTRITIONAL INTAKES AS SHOWN BY DIETARY HISTORIES*

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Recent prenatal studies indicate that faulty nutrition during pregnancy may affect the mother and her fetus in ways not usually considered to be signs of malnutrition. They provide a background for understanding the increased nutritional requirements of this period. They emphasize the importance of including evaluation of nutritional status as well as dietary advice as a routine part of prenatal care.

Table 1 gives the nutritional allowances for pregnancy (4th through 9th month) recommended by the Food and Nutrition Board of the National Research Council (1). These are shown in relation to the allowances recommended for a normal woman (sedentary) and for a lactating woman.

Before discussing our research findings as well as the results of other workers in this field, it would seem pertinent to review briefly the bases on which these nutritional allowances for the latter part of pregnancy depend. While many persons consider that they are liberal, it should be remembered that they were designed to serve only as guides. They include a margin of safety over the minimum requirement for each nutrient; (the minimum requirement is an amount which will just prevent signs and symptoms of deficiency). These allowances for pregnancy, in so far as our present knowledge of nutrition permits, represent an amount of each nutrient which would provide for the best possible health during pregnancy, preparation for labor, delivery and the postpartum period, as well as provide an environment which would permit optimum growth and development of the fetus. These allowances also presuppose that a woman enters pregnancy in optimum nutritional state which is often far from true. Although the increased requirements in the first trimester of pregnancy are so small as to be negligible, it should be pointed out that if the diet has been deficient previous to pregnancy this may prove to be a matter of considerable importance, especially if Warkany's (2) findings in relation to congenital malformations in animals should prove to be even in part applicable to human beings.

Although a single value is given to cover the energy allowance, the calorie figure varies so widely from one individual to another as to be practically valueless. It would be much better to state that in the latter part of pregnancy the caloric requirement is elevated approximately 20 per cent due to increased basal metabolic rate (3), remembering that this figure may be affected by hormonal changes occurring in pregnancy (4), and that any increase due to increased metabolic rate may be considerably offset in the latter part of pregnancy by a

approximated those later recommended by the Food and Nutrition Board of the National Research Council.

A detailed history of the dietary habits of an individual furnishes important information since his nutritional status can be no better than his past and present food habits permit, although it may be considerably worse because, for various reasons, an individual may be unable to utilize normally the food which he eats. The physician, the biochemist and the nutritionist working together as a research team, each collecting and evaluating his data independently, and then comparing the results, serve to check each other's findings. If relationships do exist, results collected in this manner can be relied upon with much greater confidence than when laboratory values, findings of dietary histories or clinical signs alone point to a deficiency. Since no dietary history can be exact, there has been a tendency to discredit this very important tool in any research which attempts to evaluate nutritional status. In many instances this criticism has been and is justified, and since a dietary history taken for research purposes is of much greater value than is generally appreciated, I should like to try to make clear to you some of its merits and pitfalls. It should be remembered that clinical signs and symptoms of deficiency, alterations in patterns of growth, physical health, endurance, frequency of illness and the like may result from either or both of the following: the average dietary intake for the period under consideration and the nutritional status of the individual prior to the period considered. Hence, the *average* dietary pattern over a considerable period becomes important for correlation with clinical and laboratory findings. This can be obtained only by the dietary history method.

In our studies we have employed a careful method of cross checking the data, which increases the accuracy of the history considerably (11). The average amount of each nutrient consumed is, therefore, represented by a calculated figure recorded in calories, grams, milligrams or International Units. Since the calculated figures give an unjustified impression respecting the accuracy of the data it is desirable to use a rating scale. The rating scale shown in Table III was used in evaluating the diets for the last two trimesters of pregnancy in our published prenatal studies. Each nutrient was rated excellent, good, fair, poor, or very poor, according to the range in which the calculated value of the average intake fell. No attempt was made to rate calories according to this scale but rather caloric intakes above 2800 were termed excessive, while those below 2200 were considered inadequate.

We assigned a mean value to the average dietary intake of each woman, which allowed us to place each case in an approximately exact relationship to every other case in this study.

An overall relationship was found to exist between a good or excellent diet during pregnancy and good physical condition of the infant at birth, and between poor maternal diet and poor physical condition of the infant as shown in Figure 1.

The cases were selected on the basis of the mother's dietary rating for pregnancy. The infants termed excellent were the best infants, by definition, those

numbers of pregnant women which have demonstrated a significant relationship between the quality and quantity of the maternal diet on the one hand and the course or outcome of pregnancy and the development of the fetus on the other. These studies in some instances have, as already stated, included evaluation of the diets of the women during pregnancy, in others known supplements were fed, while in certain countries rationing of food and other conditions brought about by war have afforded an unusual opportunity to study the effects of diet during pregnancy upon both mother and fetus. Reference should be made to one of the early studies of this type which attracted considerable attention, the study by Ebbs, Tisdall and Scott (7) carried out in Toronto, Canada. Three groups of women were studied during the last half of pregnancy. The diets of the women in one group, who had poor incomes, were supplemented to an excellent nutritional level; another group of women, whose incomes were considered adequate, were taught an excellent diet for pregnancy, while the third group remained on

TABLE II

Optimum daily nutritional requirements in pregnancy and the optimum normal requirements of the average woman

NUTRITION ESSENTIALS	NORMAL	PREGNANCY (4TH THROUGH 9TH MONTH)
Calories:	2,200–2,400	2,600–2,800
Protein, gm	60	85–100
Calcium, gm	0.8	1.5
Phosphorus, gm	1.32	2.0
Iron, mg	15	20
Vitamin A, I.U.	5,000	8,000
Thiamine, mg	1.5	2.0
Riboflavin, mg	2.0	2.5
Niacin, mg	15	18
Ascorbic acid, mg	70	100
Vitamin D, I.U.		400–800

poor diets and so served as controls. The incidence of abortions, premature births, stillbirths and neonatal deaths was significantly higher in the group on a poor diet. The women in the groups with supplemented and good diets not only had healthier babies but they themselves proved to be better obstetrical risks, they suffered fewer complications including less toxemia, and they had fewer difficulties during labor, delivery and the postpartum period. The ability of the mother to nurse her infant also appeared to be influenced by the quality of her diet during pregnancy (8).

Our study of 216 pregnant women (9, 10) drawn from the prenatal clinics of the Boston Lying-in Hospital included detailed dietary histories obtained at intervals during pregnancy. It was undertaken to determine the influence, if any, of diet during pregnancy upon the growth and development of the fetus as well as any relationship which there might be with the course of pregnancy, labor and delivery or with the postpartum period. The diets of these women were evaluated in relation to a set of nutritional standards shown in Table II which

defined as good. In this and other aspects of the subject treated below, we have been interested in certain associations between outcome or course of pregnancy and maternal diet. We do not insist and have never insisted upon any etiologic correlation between one of these items and the other. The relationship, however, continues to interest us greatly. As shown in this graph 94 per cent of the infants born to women whose diets were rated good or excellent were in good or excellent physical condition at birth. In contrast 67 per cent of the infants born to women whose diets during pregnancy were poor to very poor were in the poorest physical condition at birth (i.e. they were stillborn, or died within a few hours or days after birth, or had a marked congenital defect or were premature (under 5 lbs. at birth), or were "functionally immature"). Another 25 per cent of the infants born to mothers in the poorest diet group were in only fair physical condition at birth. In other words, 92 per cent of the women whose diets were very inadequate gave birth to infants whose condition was unsatisfactory. Eighty-nine per cent of the women whose diets received a fair rating gave birth to infants whose physical condition was either good or fair. This overall relationship between the physical condition of the infant at birth and the maternal diet is a very significant one. While it exists beyond any reasonable doubt, we are unable to explain the nature of this relationship, or the manner in which it operates. We do know, however, that in this study all of the stillborn infants, all except one of the infants who died in the neonatal period, all except one of the premature infants, and most of the infants with major congenital defects, were born to women in the poorest diet group. I should like to call your attention to the fact that these poorest infants are almost exclusively confined to the poorest diet group where the inadequacies in the diet are extreme, where, irrespective of caloric intake, there was extreme deficiency of essential nutrients, and where the amounts of various nutrients were below minimum nutritional standards. I should also like to remind you that no intensive effort was made in the majority of these cases to influence the woman to eat a better diet. It is likely therefore that in many of these cases the ratings representative of the diet during pregnancy may give a picture of the woman's food habits for a considerable period of time. In other words the woman's own nutritional state at the time she enters pregnancy, as well as the quality and quantity of her diet during pregnancy, may be a very important factor in these relationships.

Table IV shows that the average birth weight and birth length of the infants born to mothers whose diets were good or excellent was 8 lbs., 8 oz., their length 51.8 cm., in contrast to 5 lbs., 13 oz., and 47.2 cm. in the case of those infants whose mothers' diets were poor to very poor.

While no statistically significant relationship for primiparas was found between the antepartum diet and the length of labor, there were many more difficult types of delivery in the poorest diet group, despite the fact that these infants averaged almost 3 lbs. lighter in weight and several centimeters shorter in length than the infants of mothers whose diets were good or excellent.

Cameron and Graham (12) of the Glasgow Royal Maternity and Women's Hospital studied the dietary intakes of mothers of stillborn infants, mothers of

TABLE III

Nutritional standards used in rating dietary intakes during pregnancy (4th through 9th months)

NUTRITIONAL ESSENTIALS	EXCELLENT	GOOD	FAIR	POOR	VERY POOR
Protein, gm..............	85 or more	70–84	55–69	45–54	<45
Calcium, gm............	1.5	<1.5–1.0	<1.0–.75	<.75–.6	<.6
Phosphorus, gm........	2.0	The same rating was given phosphorus in each case as was assigned to protein			
Iron, mg................	20	<20–16	<16–12	<12–10	<10
Vitamin A, I.U..........	8000	<8000–6000	<6000–4000	<4000–2000	<2000
Thiamine, mg...........	2.0	<2.0–1.0	<1.0–>.5	.5–.3	<.3
Riboflavin, mg.........	2.5	<2.5–2.0	<2.0–1.5	<1.5–1.2	<1.2
Niacin, mg..............	18	No attempt was made to rate niacin			
Ascorbic acid, mg......	100	<100–75	<75–50	<50–35	<35
Vitamin D. I.U..........	400–800	These were used merely as "excellent" with added D and "poor" without added D			

(Courtesy of the Journal of Nutrition, Vol. 26, p. 569, 1943.)
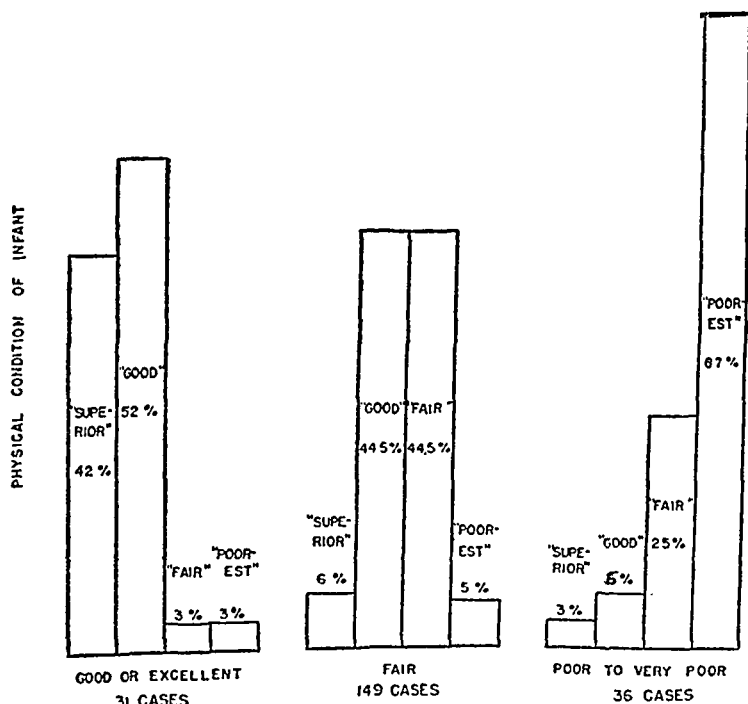
Fig. 1. Relationship of prenatal nutrition to the physical condition of the infant at birth and within first two weeks of life.

(Courtesy of the Journal of Nutrition, 26, p. 569, Dec., 1943)

against whom no physical count was found either at the birth examination or during the two-week stay in the hospital nursery. The physical condition of infants with only one or occasionally two minor physical counts against them was

Wales and Scotland the stillbirth rate has fallen during the war period and that all age groups and parities have been affected uniformly. He, as well as the other English workers mentioned, have referred to the apparent operation of some factor on a national scale and considered it probable that improvement in the diets of the poorer women is the explanation.

The effect of the maternal diet upon the complications of pregnancy is shown in Figure 2. While this relationship is significant it is less marked than the relationship with the condition of the infant at birth. Sixty-eight per cent of the women who had good or excellent diets had no complications while only 42 per cent of the women with poor diets had a normal course of pregnancy. However, a very marked relationship was found to exist between the woman's general die-
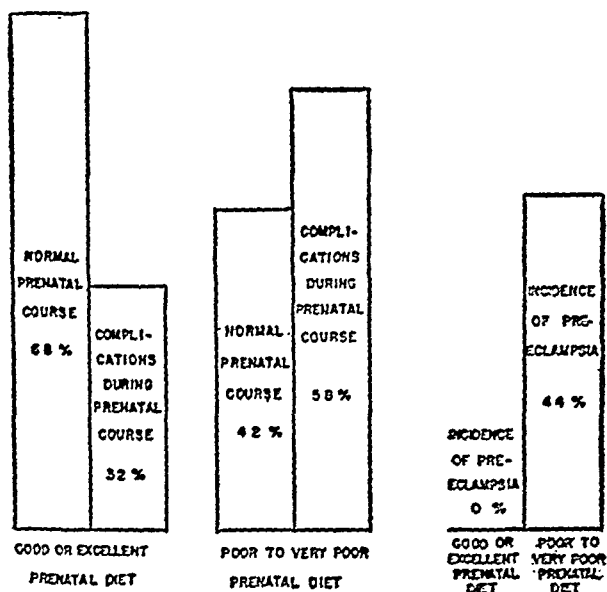
Fig. 2

(Courtesy of American Journal of Obstetrics and Gynecology, Vol. 46, p. 38, July 1943.)

tary rating and the incidence of toxemia. While there was no toxemia among the women whose diets were good or excellent, it developed in 8 per cent of the women whose diets were fair and in 44 per cent of the women in the group with the poorest diets. It is interesting to note that the incidence of toxemia fell in England under the existing conditions of rationing.

Although I cannot discuss the studies here I should like to call your attention to the interesting work which was carried out by Dr. Clement Smith of our group, in Holland in 1945 (16, 17) and to the published report of Antonov (18) of the Leningrad State Pediatric Institute of conditions during the siege of Leningrad. Both of these workers show interesting effects of inadequate nutrition resulting from war conditions on both mother and infant.

The question might well be asked: Do many women in this country have poor

prematurely born infants and an equal number of mothers of normal full term infants. The average dietary intakes of the mothers with full term infants were superior, especially in protein, calcium and phosphorus. Apparently the vitamin content of these diets was not evaluated. These workers then tested the validity of their findings by carefully supervising the diets of several hundred women attending the prenatal clinics of this hospital while an equal number of pregnant women whose diets were unsupervised served as controls; the average age and parity of the two groups were comparable. The incidence of stillbirths and premature births was significantly higher in the group with unsupervised diets. Although there were more neonatal deaths in the control group the differences in this respect were not significant.

TABLE IV

Birth weights and lengths of infants grouped according to prenatal dietary rating

	PRENATAL DIETARY RATING		
	Excellent or good	Fair	Poor to very poor
Birth weight lbs.-oz.			
Range......................	6-12 to 11-7	3-6 to 9-3	3-4 to 8-15
Average....................	8-8	7-7	5-13
Birth length cm.			
Average....................	51.8	50.0	47.2
Range......................	46.9–54.6	45.0–54.4	40.6–52.7

(Courtesy of the Journal of Nutrition, 26, p. 569, Dec., 1943.)

Under the severe restrictions imposed by war, England appears to have profited considerably with respect to health as a result of her need to utilize all available food as efficiently as possible. Despite the monotony of the diet, the average nutritional quality of the English diet improved, especially in the lower income groups. Sir Wilson Jameson (13) and others (14) have pointed out that for the first time in the history of England special food was made available to all pregnant women in the form of additional milk, eggs, supplementary vitamins and other extra rations when possible. The Ministry of Health and the Ministry of Food instituted wide spread propaganda programs for the use of these extra rations. A study of the stillbirth rates in England and Wales from 1928 through 1944 showed that a sharp drop occurred in all counties after this rationing program was instituted. In the poorest economic districts the drop has been the greatest; in Wales it amounted to approximately 35 per cent. The neonatal death rate and the prematurity rates have also declined but to a less degree. These changes occurred at a time when all conditions of life other than nutrition had deteriorated. Baird (15) discussed these same factors in Scotland and stated that the stillbirth and neonatal death rates appear to be controlled by social conditions which operate through the mother. He emphasized the fact that in England,

FIG. 3. Relation of osseous development of living full-term infants at birth to the protein content of their mothers' diets during pregnancy.
(Courtesy of Federation Proceedings, Vol. 4, No. 3, p. 271, 1945)

CALCIUM RATING OF PRENATAL DIET

FIG. 4. Relation of osseous development of living full-term infants at birth to the calcium content of their mothers' diets during pregnancy.
(Courtesy of Federation Proceedings, Vol. 14, No. 3, p. 271, 1945)

food habits? Of the 216 women studied by our group only 14 per cent consumed diets during pregnancy which could be considered excellent or good according to the nutritional standards used. The diets consumed by 46 per cent of the women were fair, 23 per cent had fair to poor diets and 17 per cent consumed diets which were poor to very poor. This means that at least 40 per cent of the women in this group were inadequately fed according to these standards during a period when the fetus undergoes rapid growth and development.

In studying the diets of these women I was impressed with the large number who did not eat sufficient amounts of protein during pregnancy if the recommended daily allowance of 85 Gms. or 1.5 Gm. per Kg. of body weight is needed. In our group of 216 women only 10 per cent had diets which could be considered excellent in protein according to this standard, while 38 per cent had diets which furnished under 55 Gm., and 14 per cent consumed less than 45 Gm. of protein daily.

TABLE V

Relationship of birth weight* and birth length to total protein in mother's diet during pregnancy (4th through 9th month)

	AVERAGE TOTAL PROTEIN (GM.)					
	Under 45	45 to 54	55 to 64	65 to 74	75 to 84	85 or more
Birth weight in pounds and ounces						
Boys.......	6–8	7–0	7–7	8–0	8–5	9–2
Girls.......	5–14	6–14	7–8	7–12	8–1	8–8
Birth length in centimeters						
Boys.......	47.6	49.3	50.2	51.4	52.0	53.3
Girls.......	46.8	48.7	49.9	50.3	51.4	52.4

* No infants under 5 pounds were included in the distribution.
(Courtesy of The Journal of Pediatrics, 23, p. 506, November, 1943.)

Table V shows the relationship of birth weight and birth length to the total protein content of the mother's diet in the group of women which we studied [19]. The length and weight of the baby at birth are very closely associated with the amount of protein in the mother's diet during the latter part of pregnancy. There was also an association with physical condition of the infant at birth which was apparent when the mother's diet contained less than 75 Gm. of protein daily.

Figure 3 shows the relationship between the protein content of the maternal diet and osseous development at birth [20]. The osseous ratings advanced, average, or retarded, refer to osseous development (i.e. the presence or absence of osseous centers in the hand, knee and foot as shown by x-rays taken at birth). Since phosphorus and certain other nutrients are closely associated with protein in food these other nutrients may be involved in this relationship. Protein, however, forms the matrix for bone growth.

Figure 4 shows the relationship between the calcium content of the maternal

FIG. 3. Relation of osseous development of living full-term infants at birth to the protein content of their mothers' diets during pregnancy.
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DISCUSSION

DR. CRAMPLIN: I wonder if anyone would care to comment upon the relationship, if any, between the diet of the mother in pregnancy and minor but often distressing symptoms such as muscle cramps, pruritis, irritation, and things of that sort.

CHAIRMAN EASTMAN: In regard to muscle cramps, I think that perhaps Dr. Dieckmann is better qualified than anyone to speak on that subject here because some years ago, if I am not mistaken, he wrote a paper on what he called subclinical osteomalacia in which he felt that those symptoms might be due to calcium and vitamin D deficiency. Am I not right about that, Dr. Dieckmann?

DR. DIECKMANN: I wrote the paper.

CHAIRMAN EASTMAN: You still believe in it?

DR. DIECKMANN: I think in the cases that we studied at that time there was very complete relief. We had these patients on metabolic studies.

Also I think a lot of the muscle cramps are the result of change in posture which results as pregnancy grows and the woman has to change the position in which she stands and is using muscles which she has not used heretofore.

DR. PAGE: This is a very minor point, but the question was raised as to the relationship

diet and the osseous rating at birth. This relationship while significant is somewhat less marked than with protein. In both of these graphs, I would call your attention again to the fact that the marked shift to a high percentage of infants whose osseous development was retarded comes in the group where the diets were extremely deficient.

While there is still controversy among well-informed persons concerning the cause of toxemia, it is generally accepted that a high protein diet does not predispose to the condition. While our group found a relationship between the general antepartum dietary rating and the incidence of toxemia, and while the protein intake was low in many of these cases, many other dietary essentials were also low, so that it was not possible to conclude that protein alone was the dietary factor involved. It should be emphasized that in human studies it is extremely difficult to prove conclusively that a given nutrient is responsible for a given effect.

I do not like to leave the subject of the protein requirement of pregnancy without reference to the important nitrogen balance studies of Macy, Hunscher and others (5) which have shown that women store normally relatively large amounts of protein during pregnancy over and above that needed by the fetus and the accessory structures. These metabolism studies indicate that a protein requirement of 845 to 900 Gm. (135 to 145 Gm. nitrogen) above maintenance is representative of the total net requirement for the fetus and its accessory structures during gestation, and that under favorable circumstances a woman retains an additional storage of 1250 to 2500 Gm. protein (200 to 400 Gm. nitrogen) as a safety factor for labor and delivery and in preparation for lactation. These figures represent an increased requirement of 10 to 20 Gm. of protein daily during the latter months of pregnancy.

It should be said that while much further investigation is needed to clarify our knowledge about the factors involved in the relationships which nutrition may bear to either mother or fetus the present evidence justifies evaluation of nutritional status and dietary advice for every woman as a routine part of prenatal care. Until our knowledge is better defined than is possible at present this should be given as early in pregnancy as possible and young women should be taught that it is important to enter pregnancy in good nutritional condition.

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once every three weeks. That factor alone may make some difference in the frequency of complications in the mother.

MRS. BERTHA S. BURKE: In answer to the question concerning the caloric intake there is a considerable difference of opinion as to whether or not it is wise to reduce an overweight woman's caloric intake exceedingly during pregnancy. I believe that it is unwise to reduce the caloric intake of the overweight pregnant woman drastically. First of all, as I have already pointed out, approximately 2000 calories of carefully selected food are required to meet the protein, mineral and vitamin needs of this period. Furthermore, if the calories are reduced below 1800 in this period there is the possibility that the woman will burn protein needed for growth to meet her energy requirement. We know from balance studies that the pregnant woman under ideal conditions stores a considerable amount of protein over and above that required by the fetus and its adnexa, supposedly as a safety factor at delivery and in preparation for lactation. How can she do this, if she is subjected to a reducing regime? Is she able to store protein in exchange for body fat? I have been unable to find an answer to this question. All I know is that if a pregnant woman gets all the essentials recommended by the National Research Council other than calories, and these are supplied by basic foods, she apparently gets along all right in the majority of instances and gives birth to a fairly large healthy baby. We have followed a considerable number of very obese pregnant patients giving them nutritional guidance at the obstetrician's request. These women cooperate well, when we spend sufficient time in the initial interviews so that they understand fully the dietary regime which is recommended. If a woman is referred to us early in pregnancy we try to hold her weight as closely as possible to her preconceptional weight, keeping her calories high enough to supply the other essential nutrients. If this is done she will weigh, when she leaves the hospital following delivery, approximately 20 to 25 pounds less than when she became pregnant. This may seem to be a rather drastic regime in a period of rapid growth and development of the fetus. The whole question certainly merits further study and consideration.

I apparently have left some in the audience confused in regard to my statement that in our study every stillborn infant, every neonatal death except one, every premature infant except one and most of the infants with congenital defects (i.e. the infants who were the "poorest" physically) were born to mothers whose diets were very deficient. In our study they fell in the poorest diet group and we have merely pointed out this fact.

In our original paper in the American Journal of Obstetrics and Gynecology, we stated in conclusion that if a woman's diet is very poor she will in all probability have a poor infant from the standpoint of physical condition and if her diet is good or excellent she will in all probability have an infant in good physical condition. This statement was made by us using the word "probability" in a statistical sense, generalizing from our findings only.

Again, I should like to say that we have never claimed a relationship between diet during pregnancy and still-births alone, or congenital defects alone, or any of those catastrophies which we have been mentioning in relation to the infant, and we have also stated only how many women in each of our diet groups had toxemia. In other words, we are saying only that these are our findings on 216 women.

I might at this point say that we are continuing to investigate in detail these relationships and are now studying all stillbirths, all neonatal deaths, all premature infants under four pounds, all major congenital defects and all non-therapeutic abortions in the Boston Lying-in Hospital. Each case is controlled by a woman of like age and parity and at the same stage of pregnancy. We believe that only in this way can we hope to have a large enough group of infants in any one of these categories to gain some additional information.

Some of you may dislike to see all stillbirths, etc. included in a study of this type. We agree most wholeheartedly that some of these cases are in no way related to diet. However, we believe that if one is to study nutrition in relation let us say, for example, to stillbirths, all stillbirths should be included. We believe that all cases in any one category should be included, because only in this way will there be a dietary history on each case. If any

between diet and muscle cramps. I think that most obstetricians have overlooked one item, namely that the higher the milk intake the greater is the frequency with which these leg cramps are complained of. Milk is relatively high in phosphorus, and we are all aware of the reciprocal relationship between calcium and phosphorus. Perhaps phosphorus is absorbed with greater rapidity or efficiency during pregnancy than in the non-pregnant state.

About 30 such women with leg cramps have been given aluminum hydroxide with their meals, for this substance is known to selectively remove phosphorus from the intestinal tract. All but one, as I recall, had complete relief of the leg cramps. Then phosphates were substituted, and the leg cramps would return. They could then be relieved by administering calcium salts other than those containing phosphorus. The dicalcium phosphate, which we so often use to supplement the diets, did not have the same effect. As a result of these clinical observations, we have discontinued the use of dicalcium phosphate, and use calcium alone. With extra calcium lactate, a high milk intake does not seem to produce the muscle irritability.

DR. A. E. RAKOFF: There is a very strong tendency on the part of some obstetricians to keep the weight down during pregnancy and to do this by cutting the caloric intake progressively, usually by trying to keep up the proteins and cutting down on fats and carbohydrates. Very often the diets of some of these patients are reduced to as much as 1200 or 1500 calories a day. I wonder if Mrs. Burke has any data which would indicate whether this is a safe procedure or not?

DR. WILLIAM J. DARBY: It is well for us to keep in mind the relative values of various techniques of nutrition appraisal and I was hoping that Mrs. Burke would say a little more about tests of the reliability of the dietary record.

Most of us who have employed dietary records or dietary histories of any sort have misgivings about them. In a few places these have been cross-checked by chemical analyses. Dr. McHenry at Toronto did such a study a few years ago and we have done a small one at Vanderbilt. In some cases it has been found that although calculated values and analyzed ones may hold similar relative positions, the calculated intake may have little absolute value. For example, it might be impossible to state from calculations that this person really took in 45, 55, or 65 grams of protein.

There are two ways of cross-checking the accuracy of calculations. One is to analyze the diets, and where it is possible this should be done. At least a sample group should be analyzed in order that other persons can place the absolute intake. Such a comparison is necessary whether one is considering data from Nashville, Chicago, Boston, or anywhere else.

There is another cross-check. There is no question that some of the nutrients which vary rapidly in the blood, like vitamin C, will be correlated with the dietary intake. If our dietary records have any significance, there should be some correlation between calculated intake and blood level of those nutrients which do fluctuate within short periods of time. It is very important to cross-check on the dietary, and I don't mean a simple cross-check between two methods of dietary calculation. Instead, there must be provided some cross-check with quantitative analytical data before we decide that any method, my method or anyone else's method of dietary recording, is an absolute procedure.

DR. Scrimshaw has mentioned earlier the influence of other factors on nutritional studies. Among these is the number of prenatal visits. The patient who conscientiously comes to the physician during her pre-natal period is going to get in less difficulty generally, or if she does get into trouble it is going to be detected earlier, than the patient who is lackadaisical about attendance at the clinic. One wonders if the patient who eats well and is conscientious about her eating is not also the most conscientious about keeping her clinic appointments.

An investigator concerned with one of the earlier studies on the effect of supplementation during pregnancy has told me that the patients who comprised their supplemental group came every week to get their supplements. He saw the unsupplemented group as I recall

DIET STUDIES IN PREGNANT PATIENTS*

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No one questions the fact that a healthy mother is more likely to give birth to a healthy infant. Good health is associated with a sufficient diet but there is a difference of opinion as to what constitutes such a diet. We have no fixed opinions as to the degree of importance of diet in pregnancy but are interested only in weighing the evidence presented by others and using our preliminary data and practical knowledge of the various problems encountered to determine the correlation of clinical and laboratory data with the food intake. Our objectives entail at present the following: (1) diet analysis and instruction; (2) a weighed or measured diet; (3) a protein intake of 85 grams or more; (4) a maximum weight gain of 8 kilos above the ideal weight.

One of us is responsible for the best care of our patients and for the training of our students and nurses, both undergraduate and graduate. It requires two full-time dietitians to give individual instruction to our patients and he must recommend, within the year, whether we need dietitians or not; but if we do require them, he must have some basis on which to justify his recommendation to the administration.

However, in order to make a sound recommendation, we need to know considerably more about what constitutes a sufficient diet, to what extent deviations affect significant laboratory and clinical findings, the extent to which the nutritional needs are being met prior to dietetic instruction, and the time and effort required to effectively change food habits. In this last area alone, much needs to be done to study effective educational procedures and methods for measuring results. Obviously we cannot expect to accomplish all these purposes in one experiment. What constitutes a sufficient diet will be determined best by a pooling of the results of many laboratories, which we hope will begin with this meeting and continue with other similar discussions at periodic intervals.

Furthermore, the extent to which changes in food habits are to be made will depend on the extent to which dietetic needs are being met prior to instruction. This will vary widely in different income levels but still more from individual to individual, depending on the family pattern of eating, nationality patterns, religious and social customs, and emotional needs. Obviously the extent to which help is needed in changing food habits can be determined most directly by taking a food history.

Much needs to be done also to study methods for changing food habits—educa-

relationship between the nutrition of the mother and stillbirths should be established those cases in which the stillbirth was from some other cause than diet would serve as natural controls. In other words you would expect to obtain a different dietary history from such cases. It is a fairer, more intelligent handling of the problem according to our statisticians.

Dr. Darby wished that I would comment further in regard to the dietary history as a research tool. I agree with him that we should use some method of checking the reliability of a dietary history. In taking such a history I use a method of cross checking the data which we believe gives a reasonably accurate history of an individual's average daily food intake. The reliability of a dietary history can be compared to some laboratory finding such as the plasma value of ascorbic acid which is known to reflect to a measurable degree the dietary intake of that nutrient. Last year at a conference in Detroit, where methods of evaluating nutritional status were being discussed, Dr. Bessey made the following statement in reference to our method of taking a dietary history: "I would like to make a comment about the value of the cross-check method as a means of determining reliability of a dietary history.......... When we did that we got a correlation so reliable that the curve of ascorbic acid based on dietary records could hardly be distinguished from those obtained by blood analysis. But if we did not use this cross-check scheme, no correlation was found." I should again like to emphasize the fact that a dietary history for research purposes is a very different type of history from that used in a clinic where one is taking a history in order to correct a patient's food habits.

guilty of malpractice when their pregnant patients developed eclampsia or puerperal infection. With these statements by Burke, Tompkins, Ebbs and others, we can foresee that doctors will soon have malpractice suits because the patient was not given proper diet instruction.

If an adequate diet is only a fraction as important as certain investigators have stated, the nutritionist is a very important part of the prenatal team. Every pregnant woman would then have to be given careful diet instruction either by a doctor or by a dietitian, preferably the latter. A sufficient number of dietitians would be available in clinics; and in the large cities the doctor would send his prenatal patients to a dietitian who would either make her own charge or would be paid by the doctor. However, if diet is not so important, and one must remember that the body is a rather foolproof machine compensating in many ways for various inadequacies in intake, it may be sufficient for the doctor to give the patient a printed outline of what she should eat and trust that she will be interested enough in herself and her unborn baby to follow his directions. On the other hand, if it is found that diet instruction and analysis are of considerable importance, it follows that certain periodic observations must be made of the patient's diet *during pregnancy* (not after delivery, when it is too late for corrective measures) to be certain that she is following instructions. It seems obvious that it is a waste of time to instruct patients if no attempt is made to determine just how effectively they follow the instructions. Irrespective of who gives the diet instruction to the mother, it will require time and will add to the already excessive cost of prenatal care. This preliminary study of a group of 100 patients illustrates the limited effectiveness of a single instruction and indicates the need for continual and repeated instruction. However, where lives are concerned, cost should not be considered but we have not reached that point in medicine in which cost is of no importance. Furthermore, funds will have to be available for supplying food to those who cannot purchase either sufficient amounts or the proper foods.

ABORTION

The average incidence of abortion is 10 per cent of all conceptions. It is generally believed that approximately $\frac{2}{3}$ of all spontaneous abortions are associated with abnormalities of the embryo or chorionic vesicle (maceration of the fetus is included under abnormalities). The remainder are due to maternal causes such as abnormal implantations of the ovum, systemic disease, tumors, anomalies of the uterus, etc. Positive proof is lacking that improper diet is an important factor. Since most abortions occur within the first three months, and since most patients do not come to the doctor until after the third month, it is obvious why most diet studies have such a low incidence of abortion. Ebbs distinguishes between "abortions" and "miscarriages" but in his study of the past obstetrical history, 51 per cent of the multiparas with a poor diet had abortions and miscarriages and 33 per cent of those with a good diet. One wonders at this high incidence of failed conceptions. His figures for the pregnancies which he studied are also questionable. Burke and her group have no abortions (preg-

tional procedures, visual aids, interviewing technics, and follow-up. This area alone requires extensive investigation with adequate, effective control groups.

In our investigation we propose to study only a small part: i.e., to determine the correlation of different levels of protein intake and caloric intake with certain laboratory and clinical findings. This report describes the methods used, the various difficulties encountered and a preliminary report of some of the data collected on 100 patients. We have reviewed previous reports, indicating what we think are errors in their methods or incorrect interpretations of data. No personal criticism is intended. Other investigators may not agree with our methods or our interpretations; knowledge is advanced by critical studies. If we can be convinced as to the value of a certain diet in pregnancy, every effort will be made to ensure such a diet for every patient, and measures will be instituted to give diet instruction to our students, nurses and doctors.

It is almost twenty years since one of us made his first balance studies on several pregnant patients and also made a survey of the dietary requirements for the pregnant woman at that time. It seems to him that comparatively little factual knowledge has been added in the past twenty years. R. C. Garry, in a review written in 1945, has a similar viewpoint, for she states: "In the 10 years which have elapsed since our previous review on nutrition in pregnancy and lactation, surprisingly few fundamental additions have been made to the scientific knowledge of the subject. If anything, on second thoughts, a more critical attitude has developed and biologists are becoming humble in face of their great ignorance of the relationship of nutrition to pregnancy and lactation. One fundamental empirical finding stands the test of time, that an ample diet of natural good foods is desirable both in pregnancy and in lactation as at other periods of life. . . . But it is quite certain that reproduction is not in itself a pathological process and that, if pregnancy and lactation seem to require inevitably routine mass therapeutic measures, then we may be sure that something is wrong with modern living, or in the interpretation of our information. . . . However, when this is all said, we must admit that we see as yet but 'through a glass darkly'."

According to several of the reports about nutrition in pregnancy, there will be no abortions, toxemia, anemia, premature deliveries, stillbirths, fetal abnormalities, etc. if the patient eats the correct diet. Furthermore, the baby will be healthy, big, strong and presumably a potential genius. No one believes this literally—certainly not the authors of these various articles—but that is what they state.

Burke and co-workers write: "Nutrition has not occupied a place of major importance as a part of prenatal care. The obstetrician's primary interest is not so much the health and development of the unborn infant as the health of the mother during pregnancy." We take exception to this statement because diet instruction, right or wrong, has been given by doctors to pregnant patients for over thirty years. The senior author can assure Mrs. Burke that the doctor is interested in having a live, healthy mother and baby, if for no other rea on than that he is more likely to collect his fee; and secondly, if he disregarded one or the other he would soon have no practice. Doctors have already been found

HEMORRHAGES

Most dietary reports have not discriminated between the various types of hemorrhage occurring in pregnancy. Since the hemorrhage in placenta previa is the result of an abnormal implantation of the ovum, it is difficult to see how diet could play any part. The majority of the cases of ante-partum abruptio placentae are associated with toxemia, and it is conceivable that the toxemia could be attributable to diet. However, these patients usually have essential hypertension, rarely preeclampsia.

FETAL MORTALITY

There has been a 35 per cent decrease in the fetal mortality for babies weighing 1000 grams or more for the period 1941–47 as compared with the preceding 10 years. Annual statistics since 1931 show a constantly decreasing fetal mortality. In approximately 15 per cent of the stillbirths and in 5 per cent of the neonatal deaths, it was impossible for either the obstetrician, pediatrician or the fetal pathologist to determine the cause of death. It is difficult to see how a proper diet could be an important factor in reducing stillbirths and neonatal deaths. If there is a constant decline in the fetal mortality, as is occurring on our Service, and if the percentages are small, it is obvious that great care must be used in the interpretation of results, even though the differences may be statistically significant.

FETAL ANOMALIES

Animal experimentation has demonstrated that extreme diet deficiencies result in some animal species in fetal abnormalities. Heredity is still the important factor in the production of minor abnormalities (cleft palate, extra digits, etc.) in human fetuses. Major anomalies have an unknown etiology. Burke and co-workers arbitrarily assign all babies with congenital malformation to the poorest group and attributed them to diet deficiency although their number are extremely small. Over a year ago a dietary history was obtained from 13 of our patients who had given birth to abnormal fetuses, but no marked dietary deficits could be noted. Major anomalies of the fetus have occurred in some of our nutrition patients who had excellent diets throughout pregnancy. Practically all malformations are believed to be determined before the eighth week of embryonic life at which time organogenesis is complete. Since the doctor and dietitian rarely see the patient before or even during this period it would seem as if diet after that time could have relatively little effect on the production of most malformations.

BABY LENGTH

It is possible by selective breeding and diet to increase the weight and stature of various animals, but heredity is still the important governing factor. Burke and co-workers believe that they have been able to increase the length of the baby by increasing the protein intake. Sontag and Wines in a recent article conclude, "There is a suggestion of a relationship between weight and length

nancies up to 28 weeks) but she states that almost all the patients were first seen after the third month.

TOXEMIA

The incidence of toxemia in hospitals in the United States varies from 0.5 to 25 per cent. The edema, proteinuria, hypertension, and associated symptoms may be due to preeclampsia, eclampsia, essential hypertension, or glomerular nephritis. Our percentages for these conditions are 38, 4, 56 and 2 per cent, respectively. The average fetal mortality due to toxemia from various clinics is 16 per cent (9 to 26 per cent). Our average fetal mortality is as follows:

Total fetal mortality
(%)

Preeclampsia: mild	6
severe	17
Essential hypertension: mild	7
severe	27
Glomerulonephritis	58

Obviously, the fetal mortality depends on the type of toxemia and on the severity. Preeclampsia occurs most frequently in the first pregnancy and diet is certainly one factor. The fact that it rarely recurs indicates that there are other important factors because the diet would in all probability be the same in subsequent pregnancies. Fetal death in patients with essential hypertension and glomerulonephritis is due to vascular lesions in the maternal placental vessels and it is difficult to conceive of any effect that diet could have on these vessels. There is a very definite connection between the incidence of toxemia and civilization. Eclampsia and preeclampsia either do not occur or are very rare in many native peoples. Dieckmann and co-workers reported that, in their complemented diet studies, two groups showed a significant decrease in the incidence of toxemia and one showed an increase. They attributed these inconsistent results to the small number of patients in each group.

ANEMIA

The hemoglobin concentration is decreased in normal pregnancy, reaching a minimum figure at 26 to 34 weeks' gestation and then increasing, but not reaching nonpregnant values until some weeks postpartum. If one uses standards for nonpregnant patients, over 60% of the pregnant patients are anemic. If one uses standards for pregnant patients, 12 per cent are anemic. Talso and Dieckmann have reported that therapeutic doses of iron in anemic pregnant patients have not caused significant increases in the hemoglobin concentration. Unreported studies by Dieckmann and Akbasli show that significant increases in hemoglobin concentration in anemia of pregnancy result from the administration of molybdenum-iron complex without any change in diet.

acterized by either little gain or a loss of weight. The average weight gain for the remainder should be a maximum of 225 grams per week.

Every patient whose total weight gain is over 10.9 kilograms does not necessarily have toxemia. Statistics do show, however, that the incidence of toxemia is increased in those patients who gain more than 13 kilograms. The total gain in pregnancy is not so important as the rate of gain. Patients who gain more than 0.6 kilograms per week have an increased incidence of toxemia, especially preeclampsia.

Under seemingly ideal conditions, balance studies would be carried out under constant supervision but this is not "home" conditions. Prior to October, 1943, diet instruction was given by one of the hospital dietitians when necessary. At that time we obtained a dietitian for half-time work in our clinics. On October 1, 1944, she became full time, and on October 1, 1945 a second full-time dietitian was added. Classes were held twice a week for the newly registered pregnant patients and the dietitians were constantly available for consultation. The services of the dietitians are available to all patients without any charge. On September 1, 1946 another dietitian was obtained and the present study was started. On April 1, 1947 another dietitian was employed to assist with diet calculations. She should be full time but can only give half her time. We have given these details to show that diet instruction adds to the cost of prenatal care. Diet study is time-consuming and very costly and should have an elastic budget. Ideally there should be no change in the clinic routine, which means that the patients are seen by a different doctor at each visit. Unfortunately this is not practical if one is carrying on an investigation. Practically all of the clinic patients in the nutrition study are seen by one, or at the most, two residents. No special control is exercised over the deliveries. Each new patient is given written instruction to see the dietitian. Approximately 10 per cent of the clinic patients and 34 per cent of the private patients do not see the dietitian. We use some coercion, but it is still disappointing that many patients refuse nutrition supervision. A third of the clinic patients and a fourth of the private patients seen by the dietitian are included in the study, which we hope will amount to at least one thousand patients by June 1, 1948. The patients chosen, with a few exceptions, meet the following conditions:

1. They are doing their own cooking.
2. They are not living with other families.
3. They are not working outside the home.
4. They have ability to follow instructions and keep reliable dietary records.
5. They are within the first four months of pregnancy.

Patients are dropped from the study when they prove to be uncooperative or if they, for any reason, become unable to keep accurate records. Data are not used if the patient has turned in less than 3 complete records during pregnancy.

On her first clinic visit the subject is loaned a 500-gram scale and taught how to use it. She is then asked to keep a complete record of everything eaten until her next clinic visit, usually an interval of two weeks. This first record is checked both qualitatively and quantitatively by further questioning, and considered a

and protein intake. Our conclusion from this study is not that protein intake has no effect upon the status of the infant at birth or during the first year, but rather that protein intake must fall below the levels current in our groups before such an effect is clearly demonstrable." A preliminary study of our data shows no correlation between length of the baby and the protein intake of the mother. One difficulty is in measuring the length of the living baby. It is very difficult for the same observer to get consistent measurements.

WEIGHT OF BABY

We have made no attempt to limit the weight of the baby by diet limitation. We believe that the evidence at hand indicates that it is extremely difficult, if not impossible, to restrict the weight of the baby by diet control. There is some evidence indicating that an excessive amount of fat will be present on babies of mothers who have an increased blood sugar.

TEETH

The statement that the mother loses a tooth for each pregnancy is false. There can be no absorption of calcium and phosphorus from the maternal teeth.

BREAST MILK

It is possible by careful selective breeding and diet controls of cattle to increase either the amount or fat content of milk. This has not been done in the human being. However, the quality of human milk has been shown to be affected by a deficient diet. The percentage of mothers with an adequate amount of milk at discharge from maternity hospitals is disappointingly low, due in great part to lack of nursing care. Most obstetricians believe that if adequate time for instruction in nursing and psychotherapy could be given by the nurses to each mother, more babies would be breast fed.

WEIGHT

We believe that the pregnant patient must have a proper diet, but this does not mean that she should have an unlimited caloric intake and as a result gain excessively in weight. The pregnant patient does not have to eat for two her own size. All studies to date indicate that the fetus at 28 weeks weighs approximately 1045 grams and that the remainder of its growth is during the last three months of pregnancy. Studies of our patients to date indicate that an increased caloric intake for the last half or last trimester of pregnancy is not necessary. As a matter of fact, *the caloric intake of some of our patients is decreased in the last trimester of pregnancy because they are less active.* We believe that the pregnant patients should be fed only in needed amounts, as an athlete is fed at the "training table"—not stuffed as if for a killing. Several studies indicate that the necessary weight gain due to the physiologic changes in pregnancy—fetus, placenta, amniotic fluid, uterus, blood volume, breasts, etc.—amounts to 6.7 kilograms. We see no need for any gain in weight greater than 8 kilograms above the ideal weight of the patient. The first three months of pregnancy are char-

acterized by either little gain or a loss of weight. The average weight gain for the remainder should be a maximum of 225 grams per week.

Every patient whose total weight gain is over 10.9 kilograms does not necessarily have toxemia. Statistics do show, however, that the incidence of toxemia is increased in those patients who gain more than 13 kilograms. The total gain in pregnancy is not so important as the rate of gain. Patients who gain more than 0.6 kilograms per week have an increased incidence of toxemia, especially preeclampsia.

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On her first clinic visit the subject is loaned a 500-gram scale and taught how to use it. She is then asked to keep a complete record of everything eaten until her next clinic visit, usually an interval of two weeks. This first record is checked both qualitatively and quantitatively by further questioning, and considered a

dietary history, since no dietary advice is given until the second visit. At that time a diet is recommended containing 85 grams of protein and other nutrients in appropriate amounts for pregnancy. For the rest of her pregnancy she is asked to weigh and record her food intake only for alternate 2 or 3 week periods. Five or 6 records are thus obtained before the end of gestation. Or since it seems less burdensome to keep more frequent records for a short period of time, many of the patients are given a choice of weighing their food one week out of three throughout pregnancy.

All subjects are seen on every clinic visit by the dietitian who saw them originally. Dietary records are calculated by four dietitians using an adaptation of the shortened method of Donelson and Leichsenring.

The following laboratory and clinical data on these patients are being recorded:

1. Height and stature of patient and husband.
2. Weight.
3. Blood pressure.
4. Urine tests for protein and dextrose.
5. Hemoglobin, hematocrit, and serum protein determinations every 2 months, on the ninth post-partum day and again at 6 weeks and 6 months.
6. Urine non-protein and creatinine nitrogen (3-day urine collections).
7. Anemia.
8. Edema.
9. Toxemia of pregnancy.
10. Duration of labor.
11. Complications of labor, delivery and the puerperium.
12. Mortality—maternal and fetal.
13. Abortions and previable prematures.
14. Baby's birth weight, length, size, nutrition and general condition.
15. Stillbirth incidence.
16. Prematurity—incidence and mortality.
17. Fetal malformations, major and minor.
18. Breast feeding.
19. Post-partum evaluation at 6 weeks and at 6 months.

The patient weighs or measures all of the food eaten, but we are calculating only the protein. Records will be available for calculation of all the minerals and vitamins. All patients are instructed on a basic diet of 1800 calories. If they gain too much, the caloric intake is reduced to 1500 or 1200, and if they require more, it is increased. The average weight of our patients near term from 1940–1943 was 67 kilograms. The mean weight gain for all patients, 1945–1946, was 9.6 kilograms, and for 204 nutrition patients was 9.5 kilograms. Thirty-three per cent of the latter group gained over 11.4 kilograms, but 34 per cent did not exceed 8.4 kilograms. The above increases are based on weight given by the patient as her normal and last clinic weight. Some of the patients seen by the dietitian have the caloric intake reduced in the last trimester because the patient is less active.

On the second nutrition conference the patient (if she lives within a radius of

10 miles) is given 3 bottles (containing preservative) and a large funnel and instructed how to collect her urine. We pick it up at her home.

Up to December 1, 1947, 875 patients were included in the study. Two hundred eighteen (29 per cent) were dropped for reasons enumerated. Three hundred twenty-eight have delivered. Six hundred thirteen patients have had from one to 3 chemical analyses of blood, and 236 have had 4 to 6. There have been one or more nitrogen and creatinine determinations of 3-day collections of urine in 262 patients.

Patients in our nutrition study have had the usual complications: abortion, premature delivery, stillbirths, fetal abnormalities, toxemia, hemorrhage, puerperal infection, etc. No attempt has been made to determine the incidence of any of the above.

All patients were repeatedly urged to use at least one quart of milk per day and to eat sufficient additional protein to give a minimum intake of 85 grams. It would seem best to us to base protein intake on a per kilogram basis instead of a standard 85 grams irrespective of the size and weight of the patient.

TABLE 1

Range of average daily intakes—100 patients—diet record no. 8

GROUP	PROTEIN		MILK		MEAT		EGGS		CHEESE (COTTAGE)*	
	Gm.	Pts.	Ml.	Pts.	Gm.	Pts.	Gm.	Pts.	Gm.	Pts.
Exc.........	85+	19	960+	15	120+	20	50+ (1 egg)	34	100+	9
I..........	60–84	55	480–959	60	60–119	65	25–49	38	50–99	15
II..........	35–59	26	30–479	25	25–59	15	0–24	28	0–49	76
Advised....	85+		1000		120+		50			

* Cheddar cheese was converted to an equivalent amount of cottage cheese.

The intakes of protein (meat, milk, eggs, cheese) of these 100 patients are given in Table I. The high per cent of low protein diets is noteworthy and is usually attributed to the high cost of these foods. However, even our staff patients pay approximately $135.00 for clinic care and 10 days in the hospital (no professional fee) and obviously have a much higher income than the usual clinic patient. In general, most of our patients have had protein intakes less than 85 grams per day and comparatively few have been able to consistently maintain an increase in the protein intake. However, if a high protein diet is important in favoring a normal pregnancy and baby, the next study should be to determine which trimester is the critical one. Obviously it would be easier to persuade patients to use additional meat, milk, cheese and eggs if it were for a limited period.

The cause of labor is unknown. I am not surprised that patients go into labor but wonder why the fetus remains in the uterus for 40 weeks. That is the enigma. Premature labor can be prevented by almost complete bed rest when the cervix shows evidence of effacement and dilatation at 28 to 34 weeks as determined by periodic vaginal examinations. Some women habitually de-

liver prematurely unless the above precautions are taken. No change in diet has ever been used except a decrease in calories because of the limited activity. Toxemia, placenta previa and abruptio placentae are responsible for many premature deliveries. Diet may be a factor in the first and possibly the latter conditions, but it is hard to conceive any relation to previa. Thus every premature baby should not be charged to a poor prenatal diet.

The duration of labor is one of the factors used to evaluate diet. Data from textbooks and several reports are given in Table II. We included criteria used for evaluating the labor: duration, amount of blood loss (placenta and episiotomy or laceration) and lacerations. One of us has been making most of these classifications while the patient is in the hospital in order that if there is any question, the responsible doctor can be interviewed. Needless to state, our labors and deliveries, as is true for most obstetric services, are properly supervised and relatively skillfully executed; thus we have very few labors or deliveries marked

TABLE II
Hours of Labor

| | TEXTBOOKS | DIECKMANN | BURKE | EBBS | | |
				Poor Diet	Supplemented	Good
Primipara....................	18	13	15.8	21.7	16.6	20.2
Multipara...................	12	7.9	10.1	11.9	10.2	10.8

Classification—Chicago Lying-in

	EXCELLENT	GOOD	POOR
Primipara—hrs...............	16	16–24	24+
Multipara—hrs...............	12	12–16	16+
Blood Loss, mls..............	<200	200–399	400+
Lacerations.................	None	Small	Extensive

"poor." A poor labor terminating in properly performed Dührssen incisions with midforceps and no excessive blood loss is classified as an excellent delivery.

Illinois law requires that all liveborn and stillborn fetuses of 22 weeks gestation or more must be reported. Two out of three of the following criteria are used to determine the maturity of the fetus:

PERIOD	AGE WEEKS	WEIGHT GRAMS	LENGTH CM.
Abortion...............	21	399	27
Previable..............	22–28	400– 999	28 –35
Premature..............	29–37	1000–2499	35.1–47
Term...................	38–42	2500–4499	47.1–54

The evaluation of the baby after it reaches the nursery is made by Dr. A. J. Hill, Assistant Professor of Pediatrics, who is in charge of the babies in our hos-

TABLE III
Pediatric ratings of newborn infants

Size*			Nutrition	
RATING	LENGTH	WEIGHT	RATING	LENGTH:WEIGHT RELATIONSHIP
	cm.	*gm.*		
"small"	<48	<2900	"thin"	length average, weight small
			"poor"	length large, weight average
"average"	48–52	2900–3900	"average"	length small, weight small
			"good"	length average, weight average
				length large, weight large
"large"	>52	>3900	"stocky"	length small, weight average
			"obese"	length average, weight large

Condition

RATING	AT BIRTH	DURING FIRST 10 DAYS
"poor" (survival unlikely)	Major anomalies incompatible with survival without treatment Extreme respiratory distress with survival unlikely Prematures under 1500 gm.	Death
"fair" (survival likely but outcome in doubt and functional result questionable)	Major anomalies compatible with survival without treatment Moderate respiratory distress with survival likely Prematures 1500–2500 gm. Immaturity	Major illness with survival (pneumonia, erythroblastosis, intracranial injury, brachial palsy, fracture, septicemia, etc.) Prolonged apathy of more than 48 hours' duration
"good" (outcome never in doubt, functional result probably excellent, minor irregularities present)	Minor anomalies (polydactylism, hypospadias, umbilical hernia, nevi, ear appendages, etc.) Mild respiratory distress without danger to life Infants over 5000 gm.	Minor illness (pyoderma, localized omphalitis, facial palsy, etc.) Feeding irregularities (poor weight gain, regurgitation, poor nursing reflexes, etc.) Apathy of less than 48 hours' duration
"excellent" (completely normal infant)	Normal, structurally and physiologically	Satisfactory on all counts

* If either length or weight is less than "average", infant placed in "small" rating; and similarly if either more than average, into "large" rating.

pital. He knows nothing of the patient's diet and evaluates the baby on the criteria given in Table III. He is familiar with the work of Burke, Ebbs and others, and these are the criteria that he thought he could use with some degree of accuracy.

Babies with gross congenital abnormalities were classified as "poorest" by Burke and co-workers and deleted by Ebbs and co-workers. Furthermore, in the "poorest" group they have included stillbirths without any limitations. Certainly some stillbirths are due to improper obstetrics (too much sedation, prolonged labor, improper anesthesia, faulty technic in the delivery, etc.). Such causes of fetal death should not be charged to diet during the preceding months.

Certainly in our hospital one cannot state that the mother who does not nurse her baby had a poor diet during pregnancy. The obstetric, pediatric and nursing staff advocate breast feeding but very little breast feeding is carried out in our institution. During the past week 130 patients were discharged, 37 per cent were nursing, 11 per cent were breast and bottle fed; 34 per cent of the patients refused to nurse, and 18 per cent could not nurse for various reasons. There are many factors concerned in whether or not the patient nurses. We believe that given an adequate number of nurses to train mother and baby in the technic of breast feeding, we would have more babies on the breast at discharge.

Turner has found for quantitative data that the weighed or measured (liquids) diet is obviously far more accurate than an estimated diet even if the estimate is made by an expert. Sontag and co-workers have made a study of the qualitative method as compared with the actual weighed diet and in their summary state that the method of the qualitative diet is reliable within such limits as are frequently desirable for certain types of group dietary studies. However, the individual intakes of calcium, phosphorus, protein and fat for their five patients, both on the qualitative and quantitative basis, show some marked discrepancies amounting in one patient to as much as 16.5 per cent; the smallest discrepancy was 2 per cent. However, there is no consistency. In some cases the estimate was less than the actual intake and in others more. We believe that studies based on diet estimates made by patients are only roughly qualitative and merely serve to indicate in a general way the type of diet consumed by the patient.

Burke, in a recent article, questioned the weighed or measured diet at home or in the hospital because it creates an artificial situation so that the person studied may not eat as he normally does. She is quite correct in her statement that unless the subjects are under 24-hour observation, there is no positive check on the kind or amount of food eaten. Yet in spite of such a statement, she is willing to accept a dietary history, although she qualifies it by stating that it must be used relatively and must be obtained by an experienced nutritionist. We do not question her statement that a diet history gives some idea of what the patient's food habits are, but memory is extremely unreliable. She has the hope that the range of her various groups is sufficiently wide so that one inaccuracy neutralizes another. We have learned during the past 16 months how difficult it is to learn just what the patient has eaten as to kind and amount, and, secondly, how much credence we can attach to her statement. Patients who have been gaining excessively but are on reduced caloric intakes, will tell you that they are not eating excessively; that there is something wrong with them because they gain weight. Obviously they are cheating, consciously or unconsciously. One cannot gain weight on air and water.

The maternal and fetal mortality during the past fifteen years for the country as a whole and certainly for most obstetric services has shown a steady and striking decrease. Data for our uncorrected maternal and fetal mortality are given in Table IV. There was a 75 per cent reduction in the maternal and a 35 per cent decrease in the fetal mortality. The prevention of maternal and fetal death on our service is in only a small part due to prenatal care; most of the deaths in the first ten years occurred during labor, delivery or the puerperium and in a recent review by the staff were classed as preventable or having preventable factors. Where maternal and fetal mortality and other complications are showing a constant decrease, it becomes extremely difficult to decide with certainty just what are the causes.

H. Oldham of our Department of Home Economics has made certain studies of riboflavin and thiamine of 11 of our primiparas of widely different social and economic backgrounds, living at home on self-selected diets. Complete urine collections were made during 7 days and on the seventh, eighth and ninth days 4-hour specimens of urine were collected for determination of riboflavin and thia-

TABLE IV

Maternal and total fetal mortality

PERIOD	DELIVERIES	UNCORRECTED MORTALITY				
		Maternal		Baby—1000 gm. +		
		No.	%	Stillbirth %	Neonatal %	Total %
Yrs 1931–41 (10)	27,321	69	0.25	1.96	1.76	3.72
1941–47 (6)	21,742	15	0.07	1.19	1.23	2.42

mine. All food eaten during these days was weighed and samples were saved for analysis. She states that the average daily intake for protein varied from 58 to 109 grams and the calories ranged from 1400 to 2300 calories.

SUMMARY

Reports of the value of an adequate amount of the proper foods in pregnancy show major inconsistencies. No one questions the fact that a healthy mother is more likely to give birth to a healthy infant. Good health is associated with a sufficient diet, but there is a difference of opinion as to what constitutes such a diet. In a preliminary study of 100 patients the protein intake of most of the women was found to be below 85 grams of protein per day. In some cases, instruction to increase the protein intake resulted in only small changes in food intake. In other cases, improvements were made.

A preliminary study of our data demonstrates the value of weighing the food intake and periodically determining the protein balance.

Studies on nutrition in pregnancy are being carried out in several other institutions. It is our hope that the results can be pooled and definite conclusions,

based on an adequate number of patients, can be made as to what foods the pregnant woman should eat.

If a proper diet is found to be of importance in pregnancy, measures will have to be provided not only for instructing the pregnant woman but for supplying the actual food supplements in many cases, as well as methods developed to determine whether or not the patient is following dietary instructions.

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DISCUSSION

MRS. BERTHA S. BURKE: I should like to comment on the recent paper of Sontag and Wines, to which Dr. Dieckmann referred and also upon Dr. Dieckmann's statement that his group also found no relation between protein intake of the mother and birth weight and length of her infant. As far as our relationship between mother's protein intake and length and weight of infant are concerned, all we can say is that our material has been most carefully collected and analyzed. If you are familiar with our group, you know it is a selected group, approximately 90 per cent Northern European stock, and that the length measurements were most carefully done. They are crown-heel lengths, where the baby is put on a measuring board, and as one of our pediatricians said, "pressed out so that you get a very close length on him." The protein was calculated in grams and represents the average or usual daily intake for the latter part of pregnancy. Dr. Smith found a somewhat similar relationship with both weight and length of infant and nutrition of mother during pregnancy in Holland. This correlation has been shown quite generally in relation to conditions of inadequate nutrition resulting from war conditions. Except possibly in the extremes, I would think that a relationship between protein intake and birth length could not be demonstrated easily unless the group is controlled racially. I do not know whether or not Dr. Sontag's Ohio group is a mixed racial group. Although it is not possible to compare our material with his in detail, since he gives no actual lengths and weights of his infants, it is clear that his group and our group are not wholly comparable. He has only 24 out of 205 women who took less than 55 grams of protein daily, while we had 81 out of 216. He has only 3 women out of 205 who consumed under 45 grams of protein, while we had 30 out of 216.

Dr. Dieckmann suggested the possibility of a printed folder about diet during pregnancy for use by the doctor or nurse, when no nutritionist is available. Our printed folder "Daily Diet During Pregnancy" is used in the Out-Patient Clinic of the Boston Lying-in Hospital. It should be individualized for the patient. Our teaching interview requires about three-quarters of an hour and at subsequent interviews we usually need to spend only a short time with the majority of the patients referred to us. It is essential that one take enough time in the first interview to teach the woman about her diet in terms of her own food habits. It is also necessary to motivate her to want to carry out the suggested changes in her diet.

CHAIRMAN EASTMAN: Is there any further comment on Dr. Dieckmann's paper? If I am not mistaken, most of, perhaps 95 per cent of Dr. Dieckmann's patients as well as Mrs. Burke's patients have been white women.

DR. DIECKMANN: All white.

MRS. BURKE: All white.

CHAIRMAN EASTMAN: In Baltimore about half of our ward patients have been colored and we have been puzzled about the behavior of these colored patients in relation to child-bearing in a number of respects. Over the past 2 decades our yearly reports show consistently year in and year out the same thing. The incidence of puerpural infection in the colored patients is twice that in the white patients. The incidence of normocytic and microcytic anemia is 3 times that in the white patients. As for premature babies, after we eliminate and put aside placenta previa, twins, eclampsia, and every conceivable cause of premature labor, and consider the remaining group who show no etiological factor responsible for the premature labor, there again, year in and year out, our incidence of prematurity among our colored patients is twice that in the white. We have been perplexed as to the factor responsible for this circumstance. It has been noted elsewhere I believe. I doubt that it is racial. It must have something to do with socio-economic conditions, living habits. We still don't have an answer. But after ruling out various possible explanations we wonder to what extent diets play a role in these differences. Some plausibility is lent to this suspicion by the fact that we still see much rickets in Baltimore.

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Afternoon Session, Saturday, January 31, 1948
Dr. George Van S. Smith Presiding

HEMORRHAGIC TENDENCIES IN TOXEMIA OF PREGNANCY
(Practical Evaluation and Management)

FOSTER S. KELLOGG

Boston, Massachusetts

It may be that there are no hemorrhagic tendencies in eclamptogenic toxemia of pregnancy per se and that such apparent phenomena are the result of shock and hemorrhage accompanying some cases of toxemia. Such evidence as I have to the contrary is meager, and speculative. Routine investigation in the manner I shall outline is essential for sound evaluation and to prove or disprove the theories I have advanced for improving clinical management.

The basic material on which these observations are made consists of 476 cases of separation of the normally implanted placenta seen in the Boston Lying-in Clinic for the sixteen years 1931–1946; 198 (41%) were considered toxic, 278 (59%) non-toxic. During this period there were 40,547 deliveries. A few other cases are used for purposes of illustration.

Last winter Hertig and I presented a paper in New York (1) in which we offered a classification of premature separation of the normally implanted placenta based on pathological study rather than clinical manifestations which was modified from the original, published in our 1945 "Lippincott Review" (2). Because this paper was not published, the classification is repeated here with two further groups added and a division of the "Toxic" group. We emphasize that the purpose of this classification is to make possible the accumulation of large amounts of data from many clinics on the basis of a commonly acceptable classification as was the case with the American Classification of Hypertensive-Albuminuric Pregnancy.

The classification follows:

(1) *Pathologic* (i.e., a laboratory finding). In these cases there are no clinical manifestations of internal or external uterine hemorrhage. Hemorrhagic infarcts are a frequent finding in the study of stillbirth placentae.

(2) *Traumatic.* In these cases the placenta is normal on pathological study. Automobile accidents, kicks in the abdomen, falls, and external version are not uncommon examples. If excessive right axis rotation is a factor in separation we believe it is invariably accompanied by some form of trauma.

(3) *Abnormal Placental or Cord Development.* (a) Placenta circumvallate and ruptured marginal sinuses are examples. In these cases pathological study of the placenta can demonstrate the abnormality. (b) Absolute short cord. This uncommon complication of the third stage of labor demands only alertness to its possibility and prompt, skillful conduct of the third stage. Relative short cord may occasionally follow external version or it may exist per se and is a purely

mechanical fetal salvage problem. Pathological study of these placentae show them to be normal.

(4) (a) *Essential Hypertension without Superimposed Eclamptogenic Toxemia.* (b) *Chronic Glomerular Nephritis without Superimposed Eclamptogenic Toxemia.* It is assumed by many obstetricians and written in text books that these patients may separate their placentae. In our study of the 476 cases we find little or no evidence that this is true. It is difficult at times to decide whether or not there exists a superimposed toxemia. We include this group in the classification so that others may help to decide the question.

(5) *Atypical Non-Toxic.* Open sinusoids at time of separation from causes unknown permit the absorption into the blood stream of endometrial, amniotic, and other types of detritus. Death, which we presume inevitable, in the one example we have, (U.H. No. 29914), was a typical shock death with non-clotting blood.

(6) *Typical Non-Toxic.* In these cases the senile degeneration of the trophoblastic-decidual junction accounts for the separation but there are no vascular changes (as in the next group). The wall of the marginal sinus, may, however, be involved in these fortuitous senile changes. This group is shown in a photomicrograph (Hertig) in the 1945 "Lippincott Review" (2).

(7) *Toxic.* In these cases arteriolar sinusoidal changes can often be demonstrated, illustrated also in the 1945 review by photomicrograph in contradistinction to group (6) (Hertig) (2).

We believe all mortality occurs in the toxic group, with a rare group (2) (traumatic) and a rare group (5) (open sinusoids) death and an occasional death from complications in the non-toxic variety. Recent study of the toxic cases demonstrates the wisdom of a subdivision (a) mild, (b) moderate, (c) severe.

Our New York paper was not published because Hertig and I felt it incomplete and that it would be possible to study subsequently all available cases of eclamptogenic toxemia as well as all types of separation of the normally implanted placenta and then to correlate each with the pathological findings.

I recapitulate suggestions hitherto made to show in what respects this question of possible susceptibility of the toxemic's blood to non-coagulability may fit into the clinical picture.

(1) Based on the first post-mortem examination of a toxic separation witnessed and a study of the literature at the time (1928) (3) I postulated that cardinal gross and microscopic pathology of typical thoroughly established toxic separation of the placenta is hemorrhage into every organ of the body, accompanied by inability of the blood to clot. That these findings occur in other types of death unaccompanied by pregnancy is well known. That similar findings may occur in pregnancy without evidence of toxemia either clinically or at autopsy our illustrative case will show. I believe these facts should not serve to discourage our effort to investigate the question in toxemia. Observed toxemias frequently afford the time for this if we will utilize it.

(2) Clinically it may be accepted with little reason for controversy that in toxic separation of the normally implanted placenta with a live baby of good neo-

natal prospects, abdominal hysterotomy is the operation of choice in the interest of that baby unless vaginal delivery is imminent. These patients do well as a rule and we are seldom confronted with the difficulties considered under (3).

(3) This reduces our problem to the group in which the baby is dead or a poor neo-natal risk, because of its size checked with its gestational age. It is in this group that controversy has arisen between proponents of the radical school, abdominal hysterotomy, and of the conservative school, rupture of membranes with or without packs, tight abdominal binder, alleged pressor free pituitary and supportive treatment including transfusion. Both schools advocate each procedure pretty much as a routine in moderate and severe toxic separation. Elsewhere (2) I have suggested on evidence presented that if we could select each case, one procedure might prove better for one, the other for another. I have suggested in detail (2) that three factors may enter into this choice, namely, (a) the condition of the blood from studies to determine a change toward inability of the blood to clot; (b) the condition of the cervix in respect to the probable length of time it will take for full dilatation—a point at times difficult to decide. When in doubt I favor abdominal hysterotomy because time presumably enters into the previous factor if it exists. (c) The amount of vaginal and cervical and at times vulval edema. If this is appreciable, the risk of disruption of tissue with cut out stitches and uncontrollable further bleeding far transcends the risk of hysterotomy. The following considerations must be emphasized at this point. (1) Toxemia and toxic separation appear as a rule at a time in pregnancy when the uterus is not prepared for labor with its accompanying ready cervical dilatation. (2) Predelivery transfusion in the presence of an open or potentially open bleeding point is a hazardous business unless such bleeding points can be quickly controlled. This hazard has on occasion led to that unpleasant situation in which more and more foreign blood has been given a patient only to be washed out with what remains of the patient's own blood—her condition being such that one did not dare stop the transfusions. My feeling is that such a patient has a better chance to survive if operated upon to stop the bleeding even when in shock or moribund, with simultaneous transfusions, than she has if we continue multiple transfusions without operation; and that hysterotomy, followed by hysterectomy when necessary, is more positive than the uterine and vaginal pack.

ILLUSTRATIVE CASES

We have selected 23 cases for consideration; 18 died, 5 recovered. These will be reported here with the utmost brevity giving only such details as we considered germane to the subject. For the most part these cases are reported chronologically but some deviation from this is made in respect to classification grouping.

Case 1. (U. H. No. 3889, Mrs. MacG., 1932). An eclamptic who had pyelonephritis in a previous pregnancy—died—no clinical separation but pathological (group I) separation at autopsy: Bilirubin 81% retention in 4 hours. She illustrates only that eclamptogenic toxemia may have group I separation.

Case 2. (Mrs. X many years ago). I sectioned this patient in the Gardiner, Massachusetts Hospital very hastily when the physician brought her in bleeding with a board-

like uterus and a slightly irregular fetal heart. She had been tossing one end of a bath towel to a dog and had suddenly fallen to the ground with excruciating abdominal pain as the doctor came out of a neighbor's house. Slicing through the abdominal wall and uterus in the buoyant manner of the day to get the baby quick, I severed the left tube one inch from its cornual entrance to the uterus. Mother and baby recovered.

This case perhaps illustrates the effect of excessive right axis rotation in connection with trauma, (Group 2). She had no evidence of toxemia.

Case 3. (U. H. No. 21211, Mrs. J., 1947)—Fell on ice. Following unsuccessful attempts at delivery from below, was delivered by vaginal hysterotomy; uncontrollable bleeding encountered; died 48 hours after entry, and 6 hours after delivery. She also had a ruptured marginal sinus. She received twenty 500 cc. transfusions before she died and it was noted that the blood clotted quickly in a tube after the 15th transfusion. She illustrates that traumatic (group 2) separations, complicated in this case by (group 3) ruptured marginal sinus may contribute to mortality; perhaps that multiple transfusion is no substitute for prompt control of bleeding source. She did not have a hysterectomy. This procedure will at times permit uncontrollable vaginal bleeding to be stopped. We note that she was not toxic and the clotting power of her blood remained until near the end.

We have no other illustrative cases of group 3 or any in group 4.

Case 4. (U.H. No. 29914, Mrs. C., 1940). This patient represents our only example of group 5, a new addition to the classification called "Atypical non-toxic" for lack of a better term. The patient had a hysterotomy for complete separation, cause unknown, followed by a hysterectomy, died four hours later and the 800 cc. of non-clottable blood in her abdomen studied seven days in the laboratory failed to clot by any known means. She was definitely non-toxic clinically and at autopsy; had endometrial and other uterine detritus in lungs, liver and presumably brain from the open sinusoids. This case appears to substantiate the Smiths' idea of the source of "Menstrual Toxin" (5, 6).

We have no examples of death in group 6, Typical non-toxic, i.e., senile degeneration of the trophoblastic-decidual junction, and are inclined to think these patients do not die.

Case 5. (U. H. No. 7197, Mrs. C., 1932). Toxic Separation—Mild Pre-eclampsia. Fetal heart was good on admission—separated placenta while undergoing "Eliminative" treatment 43 hours after admission—conservative treatment instituted for delivery from below 47 hours after admission. No labor for next 14 hours—difficult Braxton Hicks version was performed—died undelivered 12 hours later. Icteric index 30—mild jaundice increasing to severe—Couvelaire uterus.

This case may illustrate the danger of prolonged time element in this method of delivery.

Case 6. (U. H. No. 11267, Mrs. B., 1933). Eclampsia—no blood work—Toxic separation —old clots and placenta fell out—died after spontaneous normal delivery, 17 hours after delivery—no autopsy.

Case 7. (U. H. No. 21372, Mrs. C., 1937). Eclamptic—Toxic separation, 200 cc. of bright red blood, died of hemolytic streptococcus septicemia, but showed hematoma at site of veratome injections and icteric index of 45–50 before sepsis began.

Case 8. (U. H. No. 27559, Mrs. D. R., 1939). Severe—pre-eclamptic—Toxic separation on entrance—conservative delivery from below, tight cervix, internal os closed, packed, 30 hours labor—no blood work. May illustrate risk of infection with pack in a bled out patient and risk of prolonged labor because of unfavorable cervix. Autopsy findings explainable on infection basis, died of gas bacillus.

Case 9. (U. H. No. 26399, Mrs. G., 1939). Toxic separation—delivery from below of twins, stillborn—died 11th day, bilateral cortical necrosis and pituitary necrosis (7). Findings essentially same as next case.

Case 10. (U. H. No. 4344, Mrs. H., 1939). Admitted as toxic separation—delivered conservatively from below 12 hours after rupture of membranes and pack—died of cortical necrosis on seventh day post-partum (also with pituitary necrosis). At autopsy, diffuse petechial hemorrhages—Couvelaire uterus—purplish discoloration beneath bladder fold—

Prothrombin 10% of average adult level—Icteric index 18, 8, 8. After K and four trans-fusions, Prothrombin 50% (7).

Neither this case or No. 9 had excessive blood loss yet both had Simmonds Disease.

Case 11. (U. H. No. 30160, Mrs. W., 1940). Eclamptic—slight Couvelaire uterus, died in 5 hours. Toxic separation found at autopsy.

Case 12. (U. H. No. 18478, Mrs. M., 1941). Severe pre-eclamptic toxic separation. Neglected self and neglected by clinic—not sent in on earlier symptoms. Ether for pack-ing, bled from site of extracted molar during anesthesia—"Had a lot of pituitrin"—died 7½ hours after admission—bled continuously through the pack until death—hematoma at site of needle puncture—At autopsy, petechial hemorrhages in endocardium and pelvis of left kidney and bladder; hemorrhagic gastritis—Liver 2050 grams—Typical Couvelaire uterus.

Case 13. (U. H. No. 35194, Mrs. S., 1942). Prenatal neglect similar to last case. Eight days before admission, she was sent home from clinic with albumin in urine—seven days later given castor oil at home—came to clinic day of admission, B.P. 140/98, Alb. St.—passed one quart blood in clinic (out-patient)—admitted, etherized, packed, died four hours after admission "question pulmonary embolism"; stained moderately through pack until dead—no blood work—no autopsy. These two cases illustrate that all pre-eclamptics are candidates for fatal toxic separation and that hospitalization is essential on the slightest signs of toxemia.

Cases 12 and 13 were according to the conservative school of thought perfect cases for this type of delivery. Hysterotomy advocates may well believe that these patients could not have come out worse, since both died, if they had been sectioned. They might think that since both bled continuously through packs until dead, hysterotomy with or without hysterectomy and multiple transfusions might have saved them. At this point I would like to express the personal opinion that packs in the conservative treatment of toxic separation are not only a snare and a delusion but an added menace. If one elects to deliver such a patient from below, simple rupture of the membranes without the pack permits one to know what is really going on in respect to bleeding. The pack obscures the situation and I believe the pack tends to increase shock. The Spanish Windlass or tight abdominal belt comes in equally for my disfavor; it obscures the bleeding situation in the uterus. Either the uterus splints itself and delivers the baby before the mother is dead or it does not. The binder as well as the pack simply encourages pressure bleeding into the myome-trium which appears to be the major factor in the commonly noted excessive shock relative to the amount of estimated blood loss. I lack also enthusiasm for pitocin stimulation. It stimulates an already exhausted and tetanic uterus to further activity, whipping a dead horse, the theoretical result more pressure infiltration of the myometrium with blood, more shock—especially if free bleeding inside and outside the uterus is blocked by pack and tight binder. None of these phenomena takes place with hysterotomy or if the membranes are ruptured only, without pack, binder or pitocin. In 1931, Browne (8), Assistant Master at the Rotunda, showed that albuminuria appeared rapidly when confined hemorrhage from any source occurred in the body due to blood and/or destroyed tissue "toxin" and disap-peared at a speed inversely proportional to the prolongation of the time before the confined blood was evacuated, unless the kidneys were diseased. This prolonged the clearing time for albumin. He said the albuminuria was simply a visible index of what was going on in other organs of the body not visible, especially the liver, by way of endothelial damage. He cited 28 cases. The bearing of his observations on prolonging retention of confined blood in toxic separation possibly leading to irreversible changes in all organs including the blood itself, seems to me worthy of consideration, in view of our autopsy findings.

Case 14. (U. H. No. 33800, Mrs. K., 1942). Severe pre-eclampsia superimposed on hyper-tension—conservative delivery from below—died 93 hours after entrance—heavily sedated with morphine—placenta followed by 100 cc. liquid blood without clots—no autopsy—Icteric index 12—Van den Berg. 3.4.

Case 15. (U. H. No. 29883, Mrs. S., 1942). This patient was a severe pre-eclamptic. She had a history of two miscarriages and one live baby on proluton therapy. She had an elevated diastolic pressure throughout this pregnancy. She bled on March 9th, B.P.

281/84, her husband reported this on March 17th; she came to clinic on March 23rd, B.P. 136/92, checked at 162/94. Admitted to hospital; membranes ruptured, blood tinged amniotic fluid. Packed, bled 600 cc. through pack, died undelivered 13 hours and 10 minutes after entrance. She had 15 min. of pitocin, morphine, vinethene and nitrous oxide, rectal ether and paraldehyde. Vitamin K therapy. She is a replica of cases 12 and 13 and possibly the same conclusions may be drawn. No blood given for 3½ hours after entrance in shock.

Case 16. (U. H. No. 39442, Mrs. S., 1945). She was a neglected severe pre-eclamptic (para I), as she had gained 15 pounds from the 30-32 week with a 3 plus albumin and edema; sent home on magnesium sulfate by mouth. Not admitted to the hospital until the 36th week. She was watched in hospital and given 1200 mgs. of stilbestrol in 51 hours. Membranes were ruptured, went into labor, 7¼ hours to delivery, bled before delivery. Four pound, 14 ounce baby stillborn—easy outlet forceps—edematous vagina blew apart, packed twice after attempted suture—bled through pack—hysterectomy—died six hours after hysterectomy with clamps on, fibroform gauze used and uncontrollable bleeding. Thirty transfusions, only 7 of which were bank blood; 1000 mgs. Vit. C and 30 mgs. Vit. K. Autopsy, "as far as we can determine her death was caused by the blood losing its power to clot so that she had massive hemorrhages in her chest and abdominal cavity which could not be overcome by the great number of transfusions which she had." She also showed hemorrhage into virtually all her organs. The liver weighed 4780 grams. Autopsy evidence of separation—no Couvelaire uterus. "No fibrin was seen in the blood vessels except for a small amount in the liver." She bled freely from nose and mouth. She had a lot of morphine and nitrous oxide and vinethene twice.

This case illustrates the possibility of added water retention from massive doses of stilbestrol and is an example of conservative delivery from below without pack through a dangerously edematous vagina and lower segment. Stilbestrol probably has no place in the treatment of *established* toxemia. She is also an example of prenatal neglect and neglect to follow the rule that if a pre-eclamptic fails to improve, immediate interruption offers the best chance. Also, hysterectomy after the blood has become unable to clot, as well as the theoretically poor choice of anesthesia.

Case 17. (U. H. No. 37416, Mrs. S., 1943). A mild pre-eclamptic borderline to severe—no separation—held in hospital twenty-one days for twins to grow—no blood work during this period—spontaneous labor and easy breech and vertex delivery—blood loss 100 cc. at delivery—two hours after delivery, uterus soft, 300 cc. clots expressed estimated; re-softened 300 cc. clots, packed, bled through pack—died with unclottable blood six hours after delivery—seven transfusions. This case possibly illustrates that pre-eclamptics tend to fibrinolyze their blood with great rapidity since there was no cause for shock in this case; and no excessive hemorrhage in relation to replaced blood and also how little time one has on occasion to decide on and to perform hysterectomy—it being I think a sound principle that if a patient is to die of uterine hemorrhage, she should die with her uterus out and not in.

Case 18. (U. H. No. 113029, Mrs. —, 1945). This patient did not die. She was admitted after three days of bleeding at home, 15-20 pads a day, following sharp abdominal pain, a toxic separation with a marked secondary anemia. Cervix instrumentally dilated under ether anesthesia, and number 3 Voorhees bag inserted, pitocin; 27 hours later Braxton Hicks version and breech extraction under ether anesthesia. Uterine tone poor; uterus packed, pack removed in 24 hours. Immediately after delivery, temperature 103, pulse 120-150; 4 transfusions, respirations 28-36. Anuric 16 hours. Progressive jaundice—icteric index rose to 25—N.P.N. 63 mgs.%. Liver at iliac crest. Treated with hypertonic glucose, vitamin C and K and choline dihydrogen citrate. Eleventh day, icteric index and N.P.N. normal. Prothrombin level slightly elevated, red blood count 3.0 and hgb. 65%. Liver edge still palpable 2-3 cm. below costal margin. No moral is drawn from this case since she recovered; except perhaps she illustrates that a woman may have a charmed life. She had no follow-up; although one of the most interesting cases we have seen.

Case 19. Reekie's case (1942). An eclamptic without placental separation and with

slight blood loss, admitted to hospital after second convulsion, had a borderline pressure at the beginning of pregnancy, progressing upward toward the end and then a 1 plus albumin; urine boiled solid in hospital. Treated conservatively—spontaneous labor and delivery of a macerated fetus on Jan. 3, 1942 at 2 p.m.; admitted to hospital Jan. 1, 1942, hour not stated. "On the second day of hospitalization the patient developed hemorrhagic tendencies which became progressively worse in spite of use of Vitamin K, calcium and blood plasma." "Whenever hypodermics were administered, there was bleeding around the needle punctures." "She died at 1:10 p.m. January 4, 1942, approximately 68 hours after the onset of symptoms, progressively oliguric." At autopsy besides pituitary necrosis, multiple hemorrhages were found.

Case 20. (Mrs. B. M., private patient, para I, 1946). Fulminating, severe pre-eclamptic following respiratory infection. Treated four days in hospital with P.P.S. (O. W. Smith) with marked symptomatic improvement; hysterotomy for rising diastolic pressure. Beginning separation (7 x 5 cm.) found, confirmed by pathological examination of placenta. No clinical evidence. Bleeding time, coagulation time, prothrombin level within normal limits. This case may illustrate that saving time may block blood change, and as well illustrates that improved symptomatology may precede separation—as we have noted often in patients "recovering or recovered from pre-eclampsia".

Case 21. (Mrs. C., private patient, para II, 1945). Minimal or no toxemic signs and symptoms. Cervix examined one week before separation, found unfavorable for induction. Separation at home at 3:30 p.m. Section on known dead baby at 5 p.m. same day. Couvelaire uterus, complete separation, placental pathology confirmed. Operated in moderate shock, B.P. 60–70/30–40 under low spinal anesthesia. As soon as it was evident bleeding was controlled and the clot evacuated, two 500 cc. transfusions were given—normal convalescence. This case may illustrate that if the cervix is known or found to be unfavorable, hysterotomy in shock with appropriate anesthesia is the treatment of choice even on a dead or potentially worthless baby, rather than conservative delivery from below.

Case 22. (Mrs. S., private patient, delivered by Dr. Weston Sewall in my absence; para III). Lost first baby in New Hampshire with "toxemia." I delivered second baby alive at 38–39 weeks with minimal but definite signs of pre-eclampsia. This pregnancy, labor was induced two weeks before term for increasing blood pressure, albuminuria and edema. After rupture of membranes, patient began to bleed, preparations were made for hysterotomy; patient progressed rapidly; delivery from below of a living child in a few hours. Pathological report: "Premature separation of placenta; ischemic necrosis of villi." Bleeding and clotting times normal—Tourniquet test negative—other tests not made.

Case 23. (Mrs. X, case of Dr. John Newell). Patient had had a lumbo-dorsal splanchnicectomy, was to have been delivered in Providence. Separated her placenta while on trip to Boston at 7–8 months. Hospitalization somewhat slow because of other plans for delivery; fetal heart present on arrival at hospital, lost during preparation for hysterotomy—membranes ruptured, rapid labor, delivery of dead baby from below—diagnosis confirmed clinically and pathologically—normal convalescence—no blood investigation deemed necessary.

Cases 22 and 23 illustrate that delivery from below whether the baby is dead or alive (providing in this latter event the fetal heart does not deteriorate) is the method of choice if circumstances make the time certain to be reasonably short.

<div align="center">COMMENT</div>

<div align="center">*On Classification of Toxic Separations*</div>

Study of this large number of "toxic separation" (198 basic number) shows the wisdom of dividing this group into mild, moderate and severe as "pre-eclampsia" in the American Classification is divided into "mild" and "severe." The prognosis is so very different in mild and in severe pre-eclampsia; moreover in so-

called "mild pre-eclampsia" the diagnosis is most often probably not real pre-eclampsia at all.   So appears to be the case with mild as opposed to moderate and severe toxic separation based on the amount of placenta found separated on pathological study.   We shall emerge with an overall toxic separation mortality of 6–7%.   Factually mild toxic separation has little or no mortality and "mild toxic separation" as we have found is frequently open to doubt as to correct diagnosis, whereas moderate and severe toxic separation has probably carried a maternal mortality of 15–20%, at least with us under contrasting methods.of treatment and the diagnosis is far less often open to doubt.   Mild separation and pathological separation group I accompanying eclampsia carries only the eclampsia mortality.   Moreover, it is patients who are potential candidates for death whom we are interested to try to save, not the patients who get well automatically.   (For more details see forthcoming paper by Sexton and Patterson) (13).

In recent papers Smith and Smith (5, 6) state "that the fibrinolytic activity of the blood of patients with late pregnancy toxemia is, in general, more marked than that in the circulating blood of menstruating women, and appears to be related to the severity of the disease.   Willson and Munnell (10) confirmed this finding, also noting fibrinolytic activity in other conditions, but not to as marked degrees as with pre-eclampsia and hypertension with albuminuria and edema, in other words—superimposed pre-eclampsia.

I can draw no conclusion from the illustrative cases presented, except that in retrospect toxemic failure is, to again quote Eastman and Steptoe (11), lack of everlasting vigilance and wary alacrity, and my own belief that on time consuming attention frequently depend the difference between success and failure in these patients (4).   The few observations on the blood may be suggestive.

What I, and I hope others, would like to know more definitely is (a) whether or not toxemia of pregnancy per se predisposes the blood to non-coagulability or whether these deaths are from shock-hemorrhage.   Whichever is true Browne's (8) observations on "Confined hemorrhage" seem to merit more consideration than they have received with respect to clinical management.   (b) Can we by proper observation detect this change in the blood picture in time to utilize it as a "hurry-up signal" to terminate pregnancy by whatever method seems appropriate under the existing circumstances or according to the predilections of the obstetrician?

With these questions in view I offer this suggestion: That those clinics which use the American Classification of Hypertensive-Albuminuric Pregnancy, especially those which are willing, tentatively, to adopt our Classification of Separation of the Normally Implanted Placenta, in retrospect and in prospect, as for example the New York Lying-in Hospital, observe the following routine in addition to other toxemic investigation, in these groups of cases (1) in borderline mild-severe pre-eclamptics; (2) in severe pre-eclamptics; (3) in eclamptics; (4) in all placental separations, mild, moderate and severe, toxic and non-toxic; (5) in all cases of obstetrical shock and/or hemorrhage.

These tests, in so far as possible, should be made each 24 hours,
  (1) Fibrinolytic activity
  (2) Clotting time

(3) Bleeding time
(4) Number of platelets
(5) Red Cell fragility
(6) Prothrombin level
(7) Tourniquet test
(8) Needle puncture reaction
(9) Cephalin flocculation test (12)

and any other tests that appear to the hematologist or obstetrician as of aid.

I wish to acknowledge my indebtedness to Drs. Lloyd Sexton and Stuart Patterson for accumulation of data; to Dr. Sexton for a complete review and discussion; to Dr. Duncan E. Reid and Dr. Arthur T. Hertig for permission to use material which no longer belonged to me.

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DISCUSSION

DR. ARTHUR T. HERTIG: These data which Dr. Kellogg presented are certainly very unique. This is a very large series of separation of the placenta, both toxic and non-toxic. I believe his conclusions are valid and his recommendations very sound.

The thing which Dr. Sexton and I learned by going through these 476 cases of separation of the placenta was the fact that 276 of the separations were of the non-toxic variety and occurred in approximately 37,500 otherwise normal patients, whereas the remaining 200 occurred in about 2500 toxic patients. In other words, there was a distinct tendency, as I mentioned yesterday, on the part of the toxemic patient, whether mild, moderate or severe, to separate her placenta and that the more severe the toxemia the greater was the incidence of placental separation.

I think there are statements in the literature—and Dr. Sexton will correct me if I am wrong—that the average eclamptic does not tend to separate her placenta. I am sorry

that I did not think to bring an illustrative colored lantern slide which shows severe separation of the placenta in a bona fide eclamptic patient. The slide could be used either as an example of separation or of the uterus associated with an eclampsia. Actually about 40 per cent of eclamptics tend to separate their placentas with concealed hemorrhage of minor or major degrees which pass as infarction of the placenta. It is likewise perfectly true that most of those cases do not have clinical evidence of separation. What the mechanism of separation is we do not know but it is probably on the basis of spasm of the arteriolar sinusoids supplying the placenta and/or degenerative changes occurring within the walls of these sinusoids, resulting in actual destruction of endometrium, quite analogous to the process of menstruation with all its sequelae.

I was very much interested to hear what Dr. Kellogg said about the relationship of concealed hemorrhage per se to albuminuria. It is a question which should be investigated as to whether the albuminuria is a function of the toxemia in which concealed hemorrhage tends to occur or whether the concealment of the hemorrhage per se adds to the albuminuria.

DR. POMMERENKE: I would briefly call attention to the observation that in some cases of ectopic pregnancy with massive intra-abdominal hemorrhage hemoglobinuria occurs. The extent of possible renal damage has not been ascertained in our laboratories. However since this hemoglobinuria is a transitory phenomenon, it would appear to be due to a spilling over process.

DR. STANLEY GARBER: I should like to ask Dr. Kellogg to give us his classification of separations of the placenta, and I would like to ask also about the circumvallate placenta, in regard to the separation of it.

CHAIRMAN SMITH: Do you want to answer now or would you rather wait until there is further discussion?

DR. KELLOGG: I will wait.

DR. GARBER: One more comment. Having been a student once upon a time of Dr. Kellogg, I was rather impressed when I returned to Cincinnati that a great many of the cases there were treated by cesarean section. I was not satisfied with that and some years ago began selecting our cases in which the cervix was not prepared for rapid delivery by doing cesarean sections on these, but handling the others by the so-called conservative methods. We found in many cases treated by the conservative method that hysterectomy was necessary to control the bleeding. This program lowered our mortality very markedly in the last six or eight years.

DR. PAGE: It seems to me that the most essential point in this discussion is the nature of the coagulation defect which is occurring. Doctor Dieckmann, in his monograph on the toxemias, describes two cases of fatal eclampsia in which there was a complete fluidity of the blood, and in which, as I recall, analysis showed an absence of fibrinogen. An absence of fibrinogen is supposed to be a very rare cause of a bleeding tendency. If one takes most any kind of tissue, especially brain, lung or placenta—and I suppose that uterine wall could be included—and makes a saline extract of the fresh or acetone desiccated tissue, and then injects such extracts intravenously into mice, the animals will ordinarily be killed. If, however, a sublethal dose is given, then one finds that there is an incoagulability of the blood due to the fact that the thromboplastin contained in these extracts has catalyzed the formation of thrombin. The thrombin, in turn, has caused a complete defibrination of the blood. Just where all the fibrin is deposited is somewhat problematical. It may be deposited in a very widespread fashion from moving currents of blood. The liver, of course, gets its share of fibrin deposition.

It seems, therefore, that Dr. Kellogg should add to his list of tests the simple addition of thrombin to the blood to see if complete clotting occurs. If it does not, one must postulate the absence of fibrinogen, and assume that perhaps damaged tissue, like crush injury, may have liberated thromboplastin into the circulation, slowly converting the prothrombin to thrombin, then slowly converting fibrinogen to fibrin, and in time resulting actual defibrination of the blood.

According to studies made with labeled methionine, it takes the experimental animal about 8 to 10 hours to restore a depleted fibrinogen concentration; so that one would not anticipate a return of the coagulability of the blood until the liver has had this opportunity to resynthesize the fibrinogen fraction. This, of course, could be determined by an actual analysis of the blood for the various components of the coagulation system as we know them today. Perhaps Doctor Dieckmann would say more about his studies of the blood fibrinogen content in toxemia cases.

DR. KENNETH THOMPSON: There is one other factor, the possibility of heparin release. I have always been looking for that sort of a situation but never heard of the possibility until this total radiation effect was announced. That would not be too difficult to search for with the toluidin blue stains for vessels and the tissues surrounding the vessels.

DR. FOSTER S. KELLOGG: We must reconsider the work of O'Donel Browne noted in the paper in respect to Dr. Hertig's question. Browne observed (a) that albuminuria occurred in the presence of *confined* hemorrhage from any cause but particularly in toxic separation of the placenta; (b) that this albuminuria disappeared the quicker the more rapidly the blood was freed; (c) that in patients with a known hypertensive-nephritic background this disappearance time of the albuminuria was prolonged; (d) that the appearance of albuminuria is pre-eclamptic in origin, at least frequently, but that it is increased by the concealed blood or may at times be caused by it; (e) that the albuminuria is an index of endothelial damage potential throughout the body; hence by implication of the blood itself.

In view of our observations at autopsy, especially with respect to the endothelial system and the blood picture and applying Browne's theories, it seems reasonable to me that rapid freeing of confined blood is highly desirable in toxic separation and that no treatment that tends to confine the blood over long is good treatment.

The simplest way to answer Dr. Garber's question is to read the original classification as modified. May I do this?

CHAIRMAN SMITH: Yes.

The original classification and comment follows:

1. Pathologic, that is, a laboratory finding in these cases. There are no clinical manifestations of internal or external uterine hemorrhage; hemorrhagic infarcts are frequent findings in the study of stillbirth placentae.

2. Traumatic—In these cases the placenta is normal on pathological study. Automobile accidents, kicks in the abdomen, falls, and external version are not uncommon examples. If excessive right axis rotation is a factor in separation we believe it is invariably accompanied by some form of trauma, as in the case that I cited.

3. Abnormal Placental or Cord Development—which Dr. Garber asked about—in two subgroups: (a) placenta circumvallata and ruptured marginal sinuses are examples. In these cases pathological study of placenta can demonstrate the abnormality.

(b) Absolute short cord. This uncommon complication of the third stage of labor demands only alertness to its possibility and prompt, skillful conduct of the third stage. Relative short cord may occasionally follow external version or it may exist per se and is a purely mechanical fetal salvage problem. Pathological study of these placentae show them to be normal.

4. This is an added group. (a) Essential Hypertension without superimposed eclamptogenic toxemia, and

(b) Chronic glomerular nephritis without superimposed eclamptogenic toxemia.

The reason for putting that in is this: it is assumed by many obstetricians and written in text books that these patients may separate their placentae. In our study of the 476 cases we find little or no evidence that this is true. It is difficult at times to decide whether or not there exists a superimposed toxemia. We include this group in the classification so that others may help to decide the question.

5. This is the other addition and that was forced on us by a study of this material and we called it "Atypical Non-Toxic." Open sinusoids at time of separation from causes unknown permit the absorption into the blood stream of endometrial, amniotic, and other

types of detritus. This is no different from a plugged head in pelvic delivery in which there is no separation that is clinically recognizable. Death, which we presume inevitable, in the one example we have had was a typical shock death with non-clotting blood.

6. Typical Non-Toxic, illustrated by Dr. Hertig in the Lippincott Review and which I think is a very important contribution to the understanding of the whole problem of separated placenta. In these cases the senile degeneration of the trophoblastic-decidual junction accounts for the separation but there are no vascular changes, as in the next group. The wall of the marginal sinus may, however, be involved in these fortuitous senile changes.

Then there is the toxic group, and in these cases arteriolar sinusoidal changes can often be demonstrated, illustrated also in the same Review.

In this review of the pathological work which Dr. Sexton has done we were somewhat disappointed at the infrequency with which we find these changes. Is that true?

DR. HERTIG: Yes.

DR. KELLOGG: We believe all mortality occurs in the toxic group with the rare traumatic and sinusoid death, and the occasional death from the non-toxic variety.

Recent study of the toxic variety demonstrates the wisdom of dividing them for statistical purposes into mild, moderate and severe, and this division is made arbitrarily on the amount of placental separations observed in the laboratory because there is no other way that seems to be possible to do it.

Dr. Sexton and Dr. Hertig have measured this amount and ultimately their criteria for each group will appear in publication. The reason for subdivision of the toxic group, shown by the study of a large number of toxic separations, 198 basic number, is that the prognosis is so very different in mild as opposed to moderate and severe toxic separation.

We shall emerge with an overall toxic separation mortality of 6 to 7 per cent. Actually mild toxic separation has practically no mortality and mild toxic separation as we have found from a review of these records is frequently open to doubt as to the correct diagnosis, whereas moderate and severe toxic separation has probably carried a mortality of 15 to 20 per cent, at least with us, under contrasting methods of treatment. The patients who are potential candidates for death are the ones we are interested in and if we dilute our mortality down to 6%, by including a large number of mild cases which carry no mortality, we get a false picture of the potential seriousness of all toxic separations.

If anything, this paper shows two things to me. One is that most of those that died, died because they were neglected, and the second is that many of them died because the method of delivery was ill-chosen.

SOME OBSERVATIONS ON LIVER FUNCTION IN PREGNANCY

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Liver function tests in normal and toxemic pregnancy have never attained wide use; in fact, at the present time it is most uncommon for one to be performed for either diagnostic or prognostic purposes in the toxemias of pregnancy. As in 1930 little can be learned of prognostic importance from the various liver function tests in use that cannot be learned from careful clinical study. This discussion proposes to call attention again to the technique of visceral vein catheterization as a means of studying liver function. It will also point out some observations on liver function in pregnancy resulting from the use of this technique of hepatic vein catheterization. These observations will be limited to liver blood flow and to uric acid and glucose.

TECHNIQUE

For those not already familiar with the technique of venous catheterization it will be briefly described. Under local anesthesia a small incision is made in the skin overlying the median basilic vein, the vein isolated and incised and a special 100 cm. No. 8 ureteral catheter with a slightly curved through-and-through tip with one eye inserted into the vein. A continuous, isotonic saline infusion keeps the catheter from clotting. With the patient supine on a fluoroscope table, under direct fluoroscopic visualization the catheter is passed into the subclavian vein, the superior vena cava, past the right atrium, into the inferior vena cava and the right hepatic vein. The patient experiences no discomfort during the procedure. The technique has been used by several investigators and by this time many hundreds of hearts, livers and kidneys have been catheterized with no reports of fatalities or serious complications.

The lodgment of the catheter in the hepatic vein permits the withdrawal of directly efferent liver blood. Intravenous injections of test substances are not made through the catheter but through another vein in the same arm in which the catheter is inserted. The opposite arm serves as the source of samples of peripheral venous blood.

LIVER BLOOD FLOW

A method for the estimation of liver blood flow in man has been devised by Bradley and co-workers based on the "Fick" principle. The "Fick" principle may be applied to any organ to determine the blood flow through the organ if the following are known: (1) the concentration of some substance, X, in the blood entering the organ, (2) the concentration of X in the mixed venous blood leaving the organ, and (3) the total amount of X removed from the blood by the organ each minute. The blood flow through the organ per minute is then determined by dividing the total removal rate of X by the amount of X removed from each

cc. of blood as it traverses the organ. Since bromsulfalein is apparently removed from the blood stream by the liver alone, it was used as the test substance. Since it is not possible to obtain blood that is directly afferent to the liver, that is, from the portal vein and the hepatic artery, peripheral venous blood was used to represent indirectly the blood going to the liver. Since bromsulfalein is removed only by the liver, this substitution of peripheral venous blood for afferent blood to the liver is therefore permissible. Where albuminuria exists, bromsulfalein will be excreted by the kidney since it is protein bound. Thus in patients with albuminuria correction must be made for the bromsulfalein lost with the albumin through the kidney. Since there are several tributaries to the hepatic vein, samples taken through the hepatic catheter represent blood coming from only a certain portion of the liver; hence, the term, "estimated hepatic blood flow" is used.

FIGURE I

Calculation of hepatic blood flow

(after Bradley et al.—J. C. I. *24*, 890, 1945)

$$EHBF = \frac{R}{0.01 \, (P - H)} \times \frac{1}{1 - Hematocrit}$$

Where EHBF = estimated hepatic blood flow

R   = removal rate or infusion rate in mgm/minute

P   = peripheral venous concentration of BSP in mgm per 100 cc

H   = hepatic venous concentration of BSP in mgm per 100 cc

If peripheral concentration is constant,

R   = I (infusion rate in mgm/minute)

If peripheral concentration is rising,

R   = I − ($\Delta P \times V$)

If peripheral concentration is falling,

R   = I + ($\Delta P \times V$)

Where ΔP = rate of change in concentration of BSP in peripheral blood in mgm per cc per minute.

V = plasma volume in cc's.

The next slide (Figure 1) shows the formula for calculating the estimated liver blood flow. It will be noticed that the removal rate, R, of bromsulfalein by the liver is the same as the constant bromsulfalein infusion rate provided the peripheral venous concentration remains constant. But if the peripheral concentration is changing, the removal rate by the liver is then equal to the infusion rate plus or minus the rate of change in the peripheral venous concentration, ΔP, in mgms. per cc. per minute multiplied by the plasma volume. Whether to add or subtract depends inversely on whether the peripheral venous concentration is rising or falling. We found it difficult to maintain a constant peripheral bromsulfalein concentration and usually had to make this calculation. In the non-pregnant cases to be presented plasma volumes were obtained from the surface area charts of Gibson and Evans. In the pregnant patients to be presented plasma volumes were determined directly using the dye T 1824, or Evans blue, according to the method of Gibson and Evelyn.

For a complete discussion of the validity of this method reference is made to Bradley's original article in the Journal of Clinical Investigation, Vol. 24, page 890, 1945. So much for the method.

A series of 15 non-pregnant women were first examined to provide a basis for comparison and the results are shown in the second slide (Table I). The estimated hepatic blood flow varied between 1177 and 1900 cc. per minute per 1.73 M² of body surface with an average EHBF of 1548 cc. per minute. The last column in this table shows the EHBF per cent of total blood volume which ranged between 30% and 42% with an average of 35%.

TABLE I

The average EHBF in non-pregnant women with no evidence of liver disease

SUB-JECT	AGE IN YEARS	DIAGNOSIS	SUR-FACE AREA	AVERAGE SERUM CONCEN-TRATION BSP		AVER-AGE EX-TRAC-TION PER-CENT-AGE $\frac{P-\Pi}{P}$	TOTAL RE-MOV-AL RATE BSP	HE-PATIC BLOOD FLOW	HE-PATIC BLOOD FLOW	AVERAGE ΔP	PLAS-MA VOL-UME	HEMA-TOCRIT	BLOOD VOL-UME	EHBF PER CENT OF TOTAL BLOOD VOLUME
				P	Π									
			$M.^2$	*mgm. per cent*		*per cent*	*mgm. per min.*	*ml. per min.*	*ml. per min. per 1.73 M.²*					
R. S.	26	Salpingitis	1.45	.81	.28	69.1	3.92	1402	1674	.0000656	2270	39.60*	3760	37.2
R. L.	23	Salpingitis	1.69	1.03	.58	43.10	4.86	1737	1779	.0000844	2688	36.00	4200	41.3
H. M.	28	No disease	1.68	1.87	.98	45.80	6.79	1270	1307	.0002323	2688	35.70	4150	30.4
R. C.	22	Salpingitis	1.43	2.18	1.30	39.80	6.95	1706	2315	.0001236	2315	37.10	3650	38.3
F. G.	22	Salpingitis	1.58	3.80	3.23	13.95	6.59	1736	1900	.0004564	2435	38.85	4050	42.8
F. J.	32	Salpingitis	1.75	3.53	2.43	28.50	7.65	1192	1177	.0000788	2582	38.80	4220	28.2
E. S.	25	Gonococcal cer-vicitis	1.52	2.42	1.60	32.80	5.98	1385	1576	.0003530	2315	41.40	3950	35.0
G. P.	29	Post-abortal sal-pingitis	1.56	1.17	.45	59.50	5.30	1297	1438	.0008445	2635	34.50	4020	32.2
M. F.	33	Psychoneurosis	1.50	2.74	1.94	30.40	6.30	1313	1515	.0001425	2336	40.10	3900	33.6
P. T.	22	Salpingitis	1.52	1.81	.94	48.10	5.93	1203	1370	.0001000	2380	39.80	3950	30.4
M. L.	35	Bartholin cyst	1.44	1.22	.45	62.10	5.94	1298	1560	.0002770	2360	36.50	3720	34.8
M. L.	25	4 weeks postpar-tum	1.55	2.27	1.53	32.30	6.20	1264	1410	.0002150	2850	28.90	4000	31.6
L. S.	32	Salpingitis	1.38	1.64	.84	47.40	6.20	1223	1535	.0000534	2400	31.25	3490	35.0
M. W.	21	Salpingitis	1.58	2.74	1.99	26.20	6.76	1547	1695	.0001430	2780	31.40	4050	38.1
M. C.	22	25 days postpar-tum	1.67	2.21	1.20	45.40	7.68	1517	1573	.0007145	2700	35.50*	4190	36.2
Average									1548					35

* Indicates peripheral vein hematocrit. All others from hepatic vein.

Fifteen women with normal pregnancies at various periods of gestation were next examined and the results are given in the next slide (Table II). The estimated hepatic blood flow corrected to 1.73 M² of body surface area ranged from 1075 cc. to 2465 cc. per minute with an average of 1554 cc. which was practically the same average found in the non-pregnant group. The one patient, R. D., with a high flow, 2465 cc. per minute, was examined early in pregnancy, at 8 weeks. Her three previous pregnancies and the remainder of this pregnancy were perfectly normal.

Referring now to the last column of this table it will be seen that the EHBF

TABLE II

The average EHBF in normal pregnancy

SUBJECT	AGE IN YEARS	DIAGNOSIS	SURFACE AREA	AVERAGE SERUM CONCENTRATION BSP		AVERAGE EXTRACTION PERCENTAGE $\frac{P-H}{P}$	TOTAL REMOVAL RATE BSP	HEPATIC BLOOD FLOW	HEPATIC BLOOD FLOW	AVERAGE ΔP	PLASMA VOLUME	HEMATOCRIT	BLOOD VOLUME	EHBF PER CENT OF TOTAL BLOOD VOLUME
				P	H									
			M.²	mgm. per cent	per cent	per cent	mgm. per min.	ml. per min.	ml. per min. per 1.73 M.²					
M.W.	23	Para-4 Gravida-5 35 wk. gestation	1.83	2.28	1.63	29.4	6.07	1137	1075	.0006340	4460	31.60	6630	17.1
A.K.	27	Para-0 Gravida-1 40 wk. gestation	1.85	1.50	.70	52.6	6.87	1454	1360	.0000466	3533	37.30*	5760	25.2
R.D.	31	Para-3 Gravida-4 8 wk. gestation	1.45	2.59	2.10	18.1	5.63	2085	2465	.0001360	2850	40.20	4670	44.2
L.W.	34	Para-3 Gravida-4 Thr. abortion 12 wk. gestation	1.75	1.61	.89	50.2	7.10	1257	1273	.0001320	3110	36.40	5200	24.7
D.B.	26	5 mo. gestation	1.52	2.09	1.37	34.1	6.42	1319	1500	.0001030	2900	31.40	4270	30.9
A.W.	18	Para-0 Gravida-1 38 wk. gestation	1.65	2.34	1.48	36.1	6.75	1188	1245	.0001160	3080	32.30	4730	25.1
H.S.	32	Hyperemesis gravidarum 3 mo. gest.	1.58	3.02	2.61	14.1	5.67	1646	1603	.0003070	4700	22.40	6300	26.1
K.D.	23	Para-0 Gravida-1 37 wk. gestation	1.80	1.94	1.29	32.6	7.19	1520	1460	.0000205	4500	34.00	7100	21.4
E.K.	25	Para-3 Gravida-4 37 wk. gestation	1.58	3.01	2.15	28.5	6.90	1092	1196	.0002820	3680	31.10	5540	19.7
M.D.	25	Para-4 Gravida-5 Term gestation	1.73	2.12	1.56	26.1	6.49	1854	1854	.0001690	3950	34.80*	6000	30.9
M.M.	38	Thr. abortion 10 wk. gestation	1.57	3.45	2.65	23.0	6.47	1517	1672	.0002140	2350	43.80*	4200	36.1
M.S.	22	6 mo. gestation Para-0 Gravida-1	1.73	1.58	.73	52.4	7.69	1423	1423	.0000930	3350	30.10	4830	29.4
E.S.	21	Para-0 Gravida-1 7 mo. gestation	1.50	2.57	1.71	33.9	7.16	1200	1385	.0002590	3360	32.13	4950	24.2
A.F.	23	Para-1 Gravida-2 7 mo. gestation	1.70	2.61	1.86	28.1	7.86	1697	1728	.0002720	3240	33.80*	4890	34.7
A.P.	24	Bartholin abscess 6 mo. gestation	1.59	1.79	1.30	30.3	6.49	1726	1878	.0001450	3120	31.10	4520	38.1
Average								1554						28.5

* Indicates peripheral vein hematocrit. All others from hepatic vein.

per cent of total blood volume in these normal pregnancies was less than it was in the non-pregnant group with an average of 28.5% as compared with the non-pregnant average of 35%. The range was wider, from 17% to 44%. A phys-

iologic increase in blood volume in pregnancy is a known fact. With liver blood flow remaining unchanged in pregnancy, the fact that a smaller percentage of total blood volume passes through the liver is an obvious corollary; presumably, the placental bed acts as the shunt or reservoir to take care of the excess blood volume.

The conclusion then is that in spite of an increased blood volume, liver blood flow remains unchanged in normal pregnancy.

TABLE III

*The average EHBF in pregnant women with toxemia**

SUB-JECT	AGE IN YEARS	DIAGNOSIS	SUR-FACE AREA	AVERAGE SERUM CONCEN-TRATION BSP		AVER-AGE EX-TRAC-TION PER-CENT-AGE $\frac{P-H}{P}$	TOTAL RE-MOV-AL RATE BSP	HE-PATIC BLOOD FLOW	HE-PATIC BLOOD FLOW	AVERAGE ΔP	PLAS-MA VOL-UME	HEMA-TOCRIT	BLOOD VOL-UME	EHBF PER CENT OF TOTAL BLOOD VOLUME
				P	H									
			$M.^2$	mgm. per cent		per cent	mgm. per min.	ml. per min.	ml. per min. per 1.73 M^2.					
L. P.	28	Mild pre-eclamp-sia	1.6	1.85	0.60	62.9	6.72	1007	1090	.0001010	2788	40.6	4640	21.7
E. Z.	26	Essential hyper-tension	1.68	1.97	1.00	46.8	6.65	1285	1323	.0000520	3060	34.2	4490	28.6
J. M.	20	Severe pre-eclampsia pre-Caesarean	1.6	2.77	2.27	18.3	6.32	1969	2130	.0001399	2263	34.6**	3460	56.9
		10 days post-Caesarean	1.52	2.44	1.84	24.7	5.75	1736	1973	.0002575	2536	27.9	3520	49.3
A. B.	27	Hypertension with superim-posed pre-eclampsia	1.68	2.60	2.28	12.4	5.06	2374	2445	.0004154	3413	34.1	5180	45.8
A. G.	28	Nephritis 3 mo. preg-nant	1.76	1.15	0.48	58.3	6.76	1595	1568	.0000761	2286	34.3**	3480	45.8
M. F.	25	Early pregnancy (3rd) with his-tory of eclamp-sia and severe pre-eclampsia with previous pregnancies	1.82	2.29	1.88	16.2	7.65	4070	3860	.0001327	2625	39.9	4360	88.0

Turning now to liver blood flow in the toxemias of pregnancy, the next slide (Table III) is presented with full realization that the small number of cases examined precludes any definite conclusion. However, the results are rather interesting. The estimated hepatic blood flows in patient L. P. who had mild preeclampsia, patient E. Z. with essential hypertension, and patient A. G. with nephritis were certainly all within normal limits. Patient A. G., however, had severe pre-eclampsia with a fulminating course necessitating cesarean section. Examination prior to operation revealed a rather high liver blood flow, 2130 cc. per minute, which was 57% of the total blood volume; reexamination ten days after delivery showed some diminution in hepatic blood flow which had dropped

from 2130 to 1973 cc. per minute.   Patient A. B. had hypertension with super-imposed pre-eclampsia and subsequently developed premature separation of the placenta followed by delivery of a 6 lb. 11 oz. stillbirth; her liver blood flow was high, 2445 cc. per minute, which represented 46% of her total blood volume.

Most difficult to interpret is the last patient, M. F., with a liver blood flow of 3860 cc. per minute, the highest obtained, and representing 88% of her total blood volume.   The accuracy of this result could be questioned on the grounds that the catheter was not properly in the liver.   However, the position of the catheter was definitely checked during her test and seemed to be in the usual place.   This patient had a most interesting history in that her first pregnancy had been complicated by eclampsia and the second by severe pre-eclampsia. She was ten weeks pregnant in this, her third pregnancy, when her liver blood flow was estimated.   She went through the remainder of this pregnancy uneventfully and at term had a normal labor and delivery.

One hesitates even to make an assumption based on three patients; nevertheless, the *suggestion* would be that liver blood flow is altered in the severe toxemias of pregnancy with an increased blood flow through the liver comprising a higher percentage of the total blood volume.   To discuss the cause of this apparent increase would involve only conjecture and hypothesis.   Could it be due to decreased placental bed blood flow or is it the result of some other factor?   In 1932, R. H. Paramore, writing in the Journal of Obstetrics and Gynecology of the British Empire, made the hypothesis that in the toxemias of pregnancy increased intra-abdominal pressure late in pregnancy caused compression of the liver with resulting stasis in some of the liver capillaries but with an augmented flow through the remainder of the capillaries which had undergone (compensatory) distension. He went on to say that necrosis occurs in the ischemic areas while elsewhere the portal blood rushes through at such a rate that the hepatic system becomes inadequate to preserve the systemic blood from intestinal contamination.

I hasten to add that whereas in normal pregnancy the conclusion was made that liver blood flow remains unchanged, no conclusion is made as to toxemic pregnancy.   Increased liver blood flow in toxemic pregnancy is at best a suggestion, as yet inconclusive.

URIC ACID

The metabolism of uric acid in the toxemias of pregnancy has long been of interest due to its rise in concentration in the blood during pre-eclampsia and eclampsia.   In an effort to determine whether the liver were in some way responsible for this, samples of hepatic vein blood and peripheral venous blood were taken for uric acid determination concomitantly with the samples taken for bromsulfalein determinations.   Simultaneous samples were taken 8 to 10 minutes apart over a period of one hour usually.   This was done in several non-pregnant, normally pregnant and some toxemia patients.   The results are shown in the next slide (Table IV).   The figures given in the "hepatic" column represent the average of usually six samples taken simultaneously with peripheral samples, the latter also being averaged and presented in the "peripheral" column.

The last column represents the percentage difference between the hepatic vein concentrations and the peripheral vein concentrations. As can very quickly be

TABLE IV

Uric acid liver "differentials"

Based on the average of 5 or 6 samples

	DIAGNOSIS	HEPATIC	PERIPHERAL	% DIFF. $\frac{H-P}{P}$
		Mgm/100 cc	*Mgm/100 cc*	
L. Q.	Salpingitis	3.76	3.69	+1.9
R. S.	Salpingitis	3.02	2.89	+4.5
R. L.	Salpingitis	3.64	3.58	+1.7
H. M.	No disease	3.41	3.43	−0.6
R. C.	Salpingitis	2.97	2.95	+0.7
F. G.	Salpingitis	3.83	3.77	+1.6
F. J.	Salpingitis	3.89	3.85	+1.0
E. S.	G. C. Cervicitis	3.55	3.48	+2.0
G. P.	Salpingitis	2.89	2.71	+6.7
C. A.	4 Days Post-abortal	7.64	7.78	−1.8
M. W.	35 Week Gestation	3.28	3.33	−1.5
A. K.	38 " "	3.97	3.92	+1.3
L. W.	11 " "	2.36	2.31	+2.2
D. B.	22 " "	2.33	2.20	+5.9
A. W.	38 " "	3.02	2.96	+2.0
E. K.	37 " "	5.47	5.73	−4.5
M. D.	36 " "	3.49	3.40	+2.7
A. G.	12 " "	3.97	4.29	−7.5
M. F.	10 " "	2.08	2.01	+3.5
H. S.	Hyperemesis gravidarum 16-Week Gestation	7.58	7.81	−3.0
E. Z.	Moderately severe early pre-eclampsia-28 Wk. Gestation	3.63	4.18	−13.2
L. P.	Mild pre-eclampsia 36 Week Gestation	6.59	6.61	−0.3
J. M. #1	Pre-eclampsia 38 Week Gestation	6.91	6.93	−0.3
J. M. #2	10 Days post section	3.91	3.72	+5.1
A. B.	Hypertension with superimposed Mild pre-eclampsia 34 Week Gestation	4.80	4.79	+0.2

seen, no significant difference existed between the peripheral concentration and the hepatic vein concentration of uric acid in non-pregnant patients, normal preg-

nancies and a few toxemias with one exception; this exception was patient E. Z., a mild pre-eclamptic, previously presented as having a normal liver blood flow. Her average uric acid concentration was 13% lower in the hepatic vein than in the peripheral vein. No inference can be drawn from one case, obviously.

The liver is thought to be the site of uric acid destruction in man. Undoubtedly, if this is true, the rate of destruction is extremely slow and it would be impossible with present known methods of uric acid determination to demonstrate a significant difference between hepatic and peripheral concentrations of uric acid.

TABLE V

Uric acid liver "differentials" $\left(\frac{H - P}{P} \% \right)$

Following the intravenous injection of 0.5 Gm. of Uric Acid

	DIAGNOSIS	B°	TIME IN MINUTES FOLLOWING INJECTION												
			5-10	11-15	16-20	21-25	26-30	31-35	36-40	41-45	46-50	51-55	56-60	61-65	66-70	Over 70
P. T.	Mild salpingitis					-2.3		-1.2		+0.7		-4.1		+2.4		-3.4
F. H.	Complete abortion						+0.9		+1.6		+.7		+2.1		-1.9	-0.4
M. L.	Bartholin cyst	+1.2				+1.3	+4.3		+4.4	+1.3	•	0		-5.5		
L. S.	Salpingitis	-4.5					+4.4		-0.6	+0.3		+1.8		-0.9	-0.6	+1.3
M. W.	Post Abortal Salpingitis	+4.8			+12.3		+6.5		+6.9		+2.0	+1.5		+3.7		
M. C.	25 Days Post Partum	+0.4	+15.3			-17.2	+1.7		+1.9		-3.2			-11.7		
A. P.	6 Months Normal Gestation	-3.8		+4.2		+4.7	-3.1				-0.9	-4.6		-2.1		
M. S.	5 Months Normal Gestation	-3.9	+24.0			+0.5	-1.0		+3.3		-1.5		+1.2			
E. S.	7 Months Normal Gestation Para 0 Grav. 1	+5.9		+13.8			+3.5		+3.7		+1.6					
A. F.	7 Mos. Normal Gestation Para 1 Grav. 2	-8.4		+0.4	-2.0			-3.9	+1.8		-1.8					
M. M.	Threatened Abortion at 3 Mos.	-5.5	+28.0				+7.5		+7.5	+2.6		+12.5		+2.8		+20.0

The next step was to inject uric acid intravenously. 0.5 gm. of uric acid was injected intravenously and simultaneous hepatic and peripheral vein samples taken at regular intervals for about one hour. Very abruptly both sites showed an elevation of uric acid concentration. If the samples were taken very shortly after the injection of uric acid, the hepatic vein increase in uric acid concentration was found to be disproportionately higher than the peripheral. The next chart (Table V) illustrates this phenomenon which is limited to a 5 to 20 minute period following the injection, and shortly thereafter the inequality disappears and hepatic and peripheral concentrations become the same.

One hesitates to make any inference in these uric acid injection studies since the disproportionate hepatic rise within 5 to 10 minutes following injection may have been due to delayed mixing of the injected uric acid in the blood stream.

As can be seen from Table V, only six non-pregnant and five normal pregnant subjects were studied. ·No toxemia patients received uric acid injections. Further study by this method may prove illuminating.

<center>GLUCOSE</center>

Glucose was studied in a manner similar to the uric acid study. Here again simultaneous hepatic vein and peripheral vein samples were taken at regular intervals and the average hepatic and peripheral concentrations determined. Calculation of the percentage difference between the hepatic and the peripheral vein concentrations showed that glucose was almost always present in a higher

<center>TABLE VI</center>
<center>*Glucose liver differentials*</center>
<center>Based on the average of 5 or 6 samples</center>

	DIAGNOSIS	HEPATIC	PERIPHERAL	% DIFF. $\frac{H-P}{P}$
		mgm/100 cc	*mgm/100 cc*	
M. W.	Postabortal salpingitis	90	76	18
C. A.	4 days postabortal	93	93	0
M. C.	25 days postpartum	100	91	9.9
K. D.	37 wk. gestation	85	75	14
E. K.	37 " "	90	77	16
M. D.		76	70	8
A. P.	24 " "	84	82	3
M. S.	20 " "	71	66	7
E. S.	30 " "	90	85	6
M. F.	10 " "*	91	80	13
M. M.	12 " "	102	88	17
	threatened abortion			
J. M.	Pre-eclampsia—38 wk. gestation	77	68	14
A. B.	Hypertension with superimposed mild pre-eclampsia	62	56	11

concentration in the hepatic vein than in the peripheral vein. Since we know that the liver stores glycogen and converts it to glucose for distribution to the rest of the body, this is not a surprising fact. The next chart (Table VI) shows the average hepatic and peripheral concentrations of glucose and the percentage difference between the two. No significant difference was evident in subjects C. A. and A. P.; presumably at the time of study little conversion of glycogen to glucose was occurring.

The last chart, Table VII, shows the percentage difference between hepatic vein and peripheral vein concentration of glucose following the intravenous injection of 25 gms. of glucose. Here again the same early disproportionate hepatic rise in concentration is evident but again one must consider whether in the early minutes following injection this may not be due to delayed mixing. The fact that the disproportion persists in subject V. M. and was present after 11 minutes

in patient V. W. would suggest that this is not all a matter of mixing. One might infer from this chart that the sudden excess of glucose stimulates conversion of glycogen to glucose for a short period of time and that thereafter this conversion may be depressed as shown by the minus figures late in the test in three of the four subjects studied. But here again one hesitates to make inferences on a study that is so far from complete.

TABLE VII

Glucose liver "differentials" $\left(\dfrac{H - P}{P} \, \% \right)$

Following the intravenous injection of 50 cc of 50% glucose

DIAGNOSIS		B*	TIME IN MINUTES FOLLOWING INJECTION												
			0-5	6-10	11-15	16-20	21-25	26-30	31-35	36-40	41-45	46-50	51-55	56-60	61-65	65+
V.M.	Mild Salpingitis	10.7		19.1	11.2		21.7		23.8				15.4			19.5
Q.L.	Acute Salpingitis	10.6	30.7		−0.5		−3.5		1.4		4.4			−2.0		
F.P.	Salpingitis	5.9	19.2		−3.5		1.9		−4.1		−6.8			−5.1		
V.W.	Post Partum Endometritis	5.3	36.4		19.8		8.4		1.4			−3.1				

CONCLUSION

In conclusion, then, attention has been called to the venous catheterization technique permitting the taking of samples of blood directly leaving an organ, in this case the liver. Its use in pregnancy is perfectly safe.

Liver blood flow remains unchanged in normal pregnancy.

There is some suggestion that liver blood flow may be increased in the severe toxemias of pregnancy.

No significant difference exists between uric acid concentrations in the hepatic vein and the peripheral veins in non-pregnant, normal pregnant and probably the toxemia patients.

Glucose concentration is higher in the hepatic than in the peripheral veins.

No physiological conclusion can yet be drawn from this study as to liver function in the metabolism of glucose and uric acid following the intravenous injection of these substances.

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DISCUSSION

DR. HOWARD C. TAYLOR, JR.: I would like to call your attention to one possible generalization that may be emerging, namely, that many organs which we formerly regarded as

being seriously affected by pregnancy continue their function in a pretty normal manner.

It was assumed for a long time that the kidney was under a special strain during pregnancy and it was suggested that toxemia of pregnancy was due to the breakdown of the function of a perhaps "low reserve kidney" subjected to the strains of an average pregnancy. With the development of tests of glomerular function and renal blood flow it was demonstrated, however, that measurable functions of the kidney were normal in pregnancy. On the other hand, studies which have been made in several places on the kidney in toxemia of pregnancy indicate that renal blood flow is slightly increased during the toxemic period of the patient with pre-eclampsia.

The studies of the liver in pregnancy are perhaps going to follow those of the kidney. The liver also must be called upon to perform unusual functions during pregnancy. Yet at least so far as the blood flow is concerned, the liver in normal pregnancies appears from the study just presented to behave in a normal fashion. At the same time, there is a slight indication that the liver blood flow may be increased in toxemia, possibly for the same reason that it is increased in the kidney.

DR. LEON C. CHESLEY: With regard to the work on uric acid particularly, some years ago Stander and Cadden published a paper in which they stated that the best single guide to the therapy and management of pre-eclampsia is the blood level of uric acid. They believed that the rise in blood uric acid was characteristic of the disease, and that it depended upon the failure of the liver to destroy its quota of uric acid.

Actually, there is no good evidence that the human liver does destroy uric acid. This belief that it does so is based upon two lines of evidence. First, that in the dog, except for the Dalmatian coach hound, the liver does oxidize uric acid to allantoin. However, the dog does not normally excrete uric acid, and it is almost indetectable in the plasma. The dog, therefore, is not comparable with human beings in this respect. Second, uric acid fed to human beings can not be recovered quantitatively from the urine. This is probably attributable to bacterial destruction of the uric acid in the gastrointestinal tract.

Dr. Munnell's work, of course, does not indicate any destruction of uric acid in the human liver, and I am pleased to hear this direct evidence against the old belief. We have found that the renal clearance of uric acid is characteristically decreased in pre-eclampsia. Apparently the diminution depends upon two factors in these pre-eclamptics. There is a moderate reduction in the glomerular filtration rate, which pulls down the uric acid clearance. There is a second factor in that the renal tubules are over-active in reabsorbing uric acid already filtered at the glomerulus. While the filtration rate may be decreased by 15 to 25 per cent, the uric acid clearance is reduced by 30 to 50 per cent. This reduction in the clearance will account for the rises seen in the blood levels of uric acid. Other factors remaining constant, a reduction of 50 per cent in the clearance should lead to a doubling of the blood level.

DR. SIEGEL (Baltimore): I would like to ask the essayist a question with regard to his determination of blood flow. Was any attempt made to determine the excretion of bromsulfalein as a method of liver function? A number of years ago, in 1926, I studied this question of liver function in pre-eclampsia. There was some lack of function discovered as determined by the bromsulfalein.

DR. EQUINN W. MUNNELL: We did not use bromsulfalein to test liver function. Bromsulfalein to test liver function has been used in the past by several investigators and some of the severe toxemias showed some retention of bromsulfalein. We simply used the bromsulfalein as a substance that is removed only by the liver, thus giving us a test substance with which to measure liver blood flow.

THE CLINICAL MANAGEMENT OF THE LATE TOXEMIAS
OF PREGNANCY

S. A. COSGROVE AND LEON C. CHESLEY

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An enormous amount of work has been done in the search for the pathogenesis of the late toxemias of pregnancy, including the thought-provoking implications of some of the excellent studies presented at this conference. This work has covered the entire fields of biochemistry, endocrinology and allergy.

Much attention has focused on the placenta as the probable source of the disease. The most cogent evidence for this viewpoint is that hydatidiform mole, with no fetus present, carries a high incidence of preeclampsia, and occasionally exhibits eclampsia. These toxemias occur much earlier in molar than in normal pregnancies, in which living feti are present.

Page has marshalled a number of clinical observations consonant with the hypothesis that placental ischemia may be the initiating factor. Relative ischemia of the placenta might be correlated with the increased incidence of toxemia seen in primigravidae, molar pregnancies, multiple pregnancies, polyhydramnios, placental infarction, abnormal placentation, hypothyroidism and hypopituitarism. It might also be correlated to intrapartum eclampsia and the rising frequency of toxemia as pregnancy approaches term. Recently Smith and Smith have suggested that the decidua, rather than the placenta, may be the source of the eclamptogenic factor.

One of us has found that cotyledons of healthy placentae, kept alive in a Lindbergh-Carrel pump, produce an antidiuretic substance which also inhibits the renal excretion of chloride. The production of such a substance in abnormal quantities might be a determining factor in toxemia. On the other hand, we have entirely failed to demonstrate the production of any pressor substance in these cotyledons.

Chesley has found in analysis of clinical histories, evidence of a very unusually high incidence of severe toxemia in the progenitors, sisters and daughters of our severely toxic patients. We do not know whether this represents true heredity or merely environmental factors common to the several members of such families.

None of the hypotheses and suggestions even yet made, however, provides a complete answer as to the real pathogenesis of pregnancy toxemias. The same statement is true of hypertension in either pregnant or non-pregnant individuals.

So long as that remains true, the clinical classification cannot be on a wholly satisfactory basis. In order, however, that the experience of various clinics may be compared, it is probably best for the present to adhere to the classification proposed by the American Committee on Maternal Health. This recognizes two great groups of conditions:

(a) Diseases independent of pregnancy. These comprise, broadly, hypertensive disease and renal diseases which antedate the pregnancy or are observed

very early in pregnancy. They are included in the classification of toxemia because their symptom-complexes resemble those of the other type of toxemia. In the absence of a reliable history and observation in early pregnancy, clinical differentiation between them and other types of toxemia is difficult or impossible.

(b) Diseases peculiar to pregnancy, the so-called "true" toxemias of pregnancy. We may in them be dealing with a single disease rather than separate diseases, eclampsia being merely the end development of preeclampsia, exhibiting convulsions and/or coma.

Clinical differentiation between the two great groups of diseases thus outlined is frequently impossible. One cannot escape using preeclampsia, especially mild preeclampsia, as a diagnostic waste basket which holds not only true pregnancy toxemias but also unrecognized cases of hypertensive and renal disease. It is commonly thought that patients with hypertension or renal disease seem to be especially susceptible to the superimposition of the specific toxemias. Actually it is by no means certain that a hypertensive patient who shows an increase in blood pressure, proteinuria and edema does actually have superimposed preeclampsia. Hypertensive encephalopathy, with many of the clinical features of eclampsia, does occur in hypertensive men. By arbitrary definition, the finding of hypertension before the 24th week of gestation, or a reasonably reliable history of hypertension known to have antedated pregnancy, together with the exclusion of renal disease, warrants the diagnosis of hypertensive toxemia. But follow-up of patients so diagnosed, subsequent to pregnancy, will show that 15% of them do not have hypertension in the non-pregnant state, and that such a diagnosis originally arrived at will have to be abandoned or modified.

Every pregnancy, of course, represents potential hazards. But the hypertensive woman who undertakes pregnancy develops these several hazards about ten times as frequently as the woman who becomes pregnant without the prior handicap of hypertension. This ten-fold factor pertains to preeclampsia, abruptio placentae, stillbirth and maternal death. In spite of this increased potential hazard, however, it remains true that two out of three hypertensive women do escape the superimposition of specific pregnancy toxemia. There is no good evidence that otherwise uncomplicated hypertensive pregnancies leave any subsequent maternal damage or shorten the woman's life expectancy. In marked contrast to this, the one patient in three who does develop superimposed toxemia often seems to sustain lasting damage, as reflected in aggravated hypertension and shortened life expectancy.

Of the cases which we think we recognize as pure hypertensives, about half go through the entire pregnancy with essentially constant blood pressure levels. In the other half, various changes or combinations of changes are seen; in nearly 40% the blood pressure drops late in the first trimester, usually to return to the initial level or a higher one in late pregnancy. Occasionally this drop will bring the pressure down into the normal range, so that in the absence of a reliable history, the late rise will be interpreted as "pure" preeclampsia. In about 10% of cases, the blood pressure rises above its original average level early in the

second trimester. This is most ominous for fetal prognosis. When these cases show marked proteinuria, or proteinuria with increased hypertension, or edema in conjunction with either of the other triad of symptoms, it is usually interpreted as the superimposition of toxemia on the original hypertension. This occurs, as has been stated, in about one-third of the hypertensive pregnancies. The importance of the increased hazard of this superimposition of toxemia on hypertensive disease is shown in Table 1. The figures in the third column are the basis for the statement previously made that the incidences of each of these hazards in hypertensives as a complete group are roughly ten times the similar incidences found in the whole material of the clinic.

These considerations indicate the necessity of closest observation of every pregnant woman for the earliest sign of developing toxemia. This vigilance is, if possible, the more necessary in hypertensive individuals, for they are not only more likely to develop toxemia, but are likely to develop it earlier than normotensive women and in more disastrous form. In them, hopeful temporization with any degree of toxemia is dangerous and not justifiable.

TABLE 1

Hazard resulting from superimposition of toxemia on hypertensive disease

	NO SUPERIMPOSED TOXEMIA	SUPERIMPOSED TOXEMIA	ALL CASES
Foetal loss............................	18.5%	50.0%	38.2%
Abruptio placentae......................	3.8%	10.0%	5.6%
Eclampsia..............................	0	10.0%	3.0%
Immediate maternal mortality...........	0	6.7%	2.0%
Late puerperal deaths (1 to 4 mos.)......	0.9%	5.5%	2.3%
Remote annual death rate...........	14.24 per M	43.25 per M	24.82 per M

The standard nomenclature classifies the "true" toxemias as mild preeclampsia, severe preeclampsia and eclampsia. From the standpoint of management it may be well to designate them rather as the non-convulsive toxemias and the convulsive toxemias, for while management of all has a common basis, there is a sharp difference of attitude and detail as soon as any of them has become actually convulsive or comatose.

Since the definite pathogenetic factors of hypertensive disease, specific pregnancy toxemias and renal disease have not yet been fully satisfactorily determined, there can be no specific prophylaxis of these diseases. Indeed when the hypertensive pregnant woman first comes under observation her disease entity is already established and no prophylaxis is applicable to her.

In normal pregnant women not exhibiting old disease, however, the establishment of a common-sense hygienic regime will undoubtedly have some definite prophylactic value as regards specific pregnancy toxemia. That regime should include the avoidance of dietary over-indulgence both as to quantity, but very specifically as to excess carbohydrate and excess sodium chloride embodying the

mischievous sodium ion. This is not because the carbohydrate is specifically deleterious, but the limitation of excessive weight-gain is of some mechanical value with reference to the delivery and, if such dietary limitation as has been indicated fails to maintain weight gain within reasonably minimal limits, the assumption may be the more promptly arrived at that the gain is due to occult water-retention which is one of the manifestations of developing toxemia. In the healthy subject exercise within the limits of reasonable toleration is a contribution to the hygiene of the pregnant woman as well as to that of any other individual.

Correction of abnormal factors pertaining to the thyroid, to estrogen, and to progesterone as such disturbances may be demonstrable, would be at least hypothetically worth while. One of us believes that alcohol should be essentially interdicted and that tobacco consumption should be reasonably minimized. Having established all pregnant women on this common basis of hygienic regime, each of them should be carefully watched for significant changes in her condition. As already indicated, this watchfulness is, if possible, more significantly necessary in the known hypertensive group than in the normotensive group. Not only must blood-pressure observations be made frequently, but more significantly, the trend of repeated blood pressure readings should be carefully observed. In normotensive women the appearance of hypertension as indicated by rises above the arbitrary limits of 140 mm. of mercury for the systolic reading and 90 mm. of mercury for the diastolic reading, necessitates closer observation and sharp limitation of activity. In hypertensive patients sudden or continuing trend toward higher values, calls for immediate invaliding of such patients by bed rest, best exemplified in the absolute control in this regard attainable only by the hospitalization of the patient or the imposition of essentially hospital personnel control in the home.

Sudden weight gain, or too rapid continuing weight gain, especially if the dietary regulations already mentioned have been meticulously maintained, is to be interpreted as edema, whether or not accompanied by clinically demonstrable edema of any degree whatever. The appearance of this sign either in occult or gross form necessitates withdrawal of all salt from the food to the utmost degree practicable. This practical degree probably means the reduction of salt content of the daily dietary to about two grams. There is a possibility that attempts now being made in our clinic toward a more ideal limitation of dietary sodium chloride may attain a practical reduction of this factor to about half a gram a day. Total bed rest also must be enjoined under these circumstances.

Proteinuria occurring either alone or in combination with the other two symptoms already dealt with, indicate the same general principles of management. The physician at this stage of illness, has to depend almost wholly on his observation of this triad of symptoms for his estimate of the patient's condition. Eye-ground changes should, of course, be looked for, but are rarely evident at this stage. Blood chemistry changes are not generally found in significant degree. Again in regard to the value of this type of observation, greater sig-

nificance attends appreciation of shifting trends than on absolute values of any isolated observation.

In consistence with perhaps the majority of current opinions we believe that these patients should have an abundant water intake, because we do not believe that the amount of water ingested either affects the distribution of water as between the blood and tissues or has any effect on the kidneys except to increase the efficiency of the elimination of those substances which they normally do eliminate. Besides the effect of the restriction of sodium, in mobilizing water in the tissues, its transference to the blood stream and its elimination through the kidneys, ammonium chloride or potassium chloride probably aids this transfer. Of the two, we have experience only with ammonium chloride. The common method of administering ammonium chloride in enteric coated pills is perhaps, not as efficient as its administration in gelatin capsules, in spite of the somewhat increased risk of gastric irritation involved in this method. Many times the enteric coated pills do not dissolve in the intestines and at least some of the ammonium chloride is lost by its elimination through the bowel.

Mild sedation with barbiturates or with the bromides other than sodium bromide is indicated symptomatically with reference to each patient's nervous condition, rather than as part of the actual treatment of her toxemia.

If the therapy so far exhibited is going to be in any degree successful, the response of the patient in amelioration of all of the symptoms discussed, should be prompt enough to be encompassed within two or three days time. If such improvement does not occur, the final definitive resource of treatment, that is to say, the termination of pregnancy, should be promptly carried out. We have shown in another communication that to allow the pregnant woman exhibiting established toxemia, not responding to therapy, to remain in increasing jeopardy of her own life in the supposed interest of the survival of her fetus, is a futile hope. The mother's illness with all its jeopardy to her, represents at least as much, if not a greater jeopardy to her fetus. We are convinced that at least after the thirty-fifth week of fetal life, dallying with the mother is no kindness to the fetus. Rather, its chance of survival outside the womb, before it has been too much damaged by the mother's illness, is better than its chance of life in the womb subject to the rapidly increasing hazards which threaten the mother.

The manner of termination of the pregnancy under these circumstances is a technical detail which it is hardly proper to discuss extensively in this very brief review. In general our tendency is, when simple methods of medical induction have failed, to resort to prompt radical surgical emptying of the uterus.

In the marked hypertensives not exhibiting proteinuria and water retention, hospitalization during the last two months of pregnancy is advisable even though there be no aggravation of their hypertensive pattern. Here the mother's illness does not necessarily constitute any particular hazard to the fetus, except those inherent in accidents to which the mother is liable. These accidents are specifically the hemorrhagic accidents which Dr. Kellogg has already discussed with you. In anticipation of the possibility of these accidents the woman should be hospitalized under constant medical surveillance. Blood should be crossed-

matched with hers and this cross-matching should be repeated so that as particular bloods reserved for her become out-dated, new ones may be supplied, to the end that there is always immediately available for her potential needs an abundant supply of blood to replace any possible loss of blood which she may sustain. Thus protected, these patients may be temporized with in the fetal interest until spontaneous labor occurs or until the first sign of danger necessitates rapid radical intervention.

To restate very briefly what has already been said, our attitude in preeclampsia with regard to the termination of pregnancy may be designated as radical. In regard to uncomplicated hypertensive pregnancies the attitude is inclined to be conservative, unless accidental factors force radical intervention.

With the onset of convulsions and/or coma, the entire philosophy of management changes. These women are in imminent danger of death due to profound disturbance of the central nervous system, and other visceral pathologies dependent partly on a toxemia so intense as to cause the central nervous disturbance, partly directly secondary to the latter. The woman is too sick to tolerate obstetric interference of any sort. Consistent therefore with the principle that in all medical diseases complicating pregnancy, the pregnancy should be ignored and therapy should be concentrated on the appropriate management of the medical complication, all effort is directed in this situation to the overcoming of the symptoms of the severe disturbance present, completely ignoring the very fact that the woman is pregnant.

Therapy is purely symptomatic. The patient should be isolated, every possible source of direct stimulation of nervous response should be avoided, constant special nursing must be provided, restraint must be avoided except that minimally necessary to prevent serious self-injury, all gastric intake, except water during lucid intervals, should be stopped. Parenteral administration of water and glucose in hypertonic solution should be employed up to the limit of 75 to 100 grams of sugar every four hours. This is used for its diuretic effect, correction of acidosis, the buffering of the liver against glycogen depletion, and perhaps for the reduction of cerebral edema. While we are not prepared to gainsay the opinion of those who believe that rather drastic bowel elimination is an essential part of the control of this condition, we have not included it as one of the major details of our own management.

For the treatment of high degrees of oliguria which frequently accompany or follow eclampsia, there has recently been suggested the salutary availability of concentrated blood plasma. We have had no experience with this expedient nor are we inclined to include it in routine regimes of treatment, but we think that it should be borne in mind as an occasional expedient.

Finally there is the symptomatic control of the actual central nervous explosion. This is final only in our thought as to constructing an organized regime of treatment. Practically it may be frequently the primary essential of treatment.

Every possible type of sedative has been from time to time employed for this purpose. Stroganoff who has ostensibly perhaps the best mortality record ever attained in the treatment of large series of eclampsia, depended principally upon

morphine, chloroform and chloral for his medicinal triad. Each of these agents has come under such severe condemnation by various observers and practitioners that it is probable that the classical Stroganoff treatment is not practiced anywhere in this country. All kinds of schemes of sedation are designated "modified" Stroganoff methods. Chloroform has become anathema in nearly all American Clinics. Chloral, closely related to it chemically and pharmacologically, has also very largely dropped out of use.

Our own practice at present includes morphine, generally restricted to one moderate initial dose; very rarely in severe rapidly recurring convulsions, chloroform in minimal amounts; magnesium sulphate intravenously in two-gram doses, repeated at intervals of from one to six hours, depending upon the frequency of convulsions and general condition of the patient. In spite of the alarm in some quarters as to the effect of magnesium sulphate in terms of several dangers, apparent safety and efficacy of this drug in our hands emboldens us to continue to depend upon it. Others of our staff use various barbiturates instead of magnesium sulphate.

As one who practiced during the period in which veratrum viride was the sheet anchor of treatment of eclampsia, and who subsequently saw it completely discarded so far as large organized clinics in this country are concerned, we have been a little reluctant to recognize the recrudescence of this ancient enemy-disguised-as-a-friend in the new disguise of veratrone; therefore, we have no personal experience with veratrone and its use by others in our clinic has been very limited.

We believe that oxygen is a very important adjuvant in the management of eclamptics, best employed in the form of maximum concentration in an oxygen tent. We are further inclined to attach value to digitalis as an agent which probably has some effect in minimizing the risk of the cardiac collapse which kills so many of these patients. As the frequency of convulsions diminishes and the patient's sensorium and general condition improve, resumption of oral feedings must be cautiously resumed and the intensity of sedative treatment curtailed as rapidly as improvement warrants. If the pregnancy persists after the eclamptic crisis has ended, the question will arise as to the disposition of the pregnancy. We believe that the patient has now reverted to the status of severe preeclampsia and that the persistence of the pregnancy is just as great a potential danger as though she were in the same condition without having incurred a convulsive explosion. The indication for the termination of pregnancy is valid, lest her toxemia, under the influence of the continuing pregnancy, again become aggravated and even result in renewed explosive crisis. Therefore, we believe that once she has improved enough to be an acceptable surgical risk, the pregnancy should be terminated by radical operative interference, especially if the baby be still alive.

RECAPITULATION

1. Certain phases of pathogenesis of the late toxemias of pregnancy, their classification and the relation between the two great groups thereof, namely, the hypertensive types and true preeclampsia, are discussed.

2. The hazards of these conditions for the mother and for the fetus are dis-

cussed, with particular stress on the fact that the salutary effect of terminating the pregnancy when indicated is parallel with reference both to the mother and to the fetus.

3. It is suggested that for purposes of therapeusis, a very simple division into the non-convulsive and convulsive groups will suffice as a working classification.

4. In the management, a limited but definite prophylaxis is possible.

5. The importance of close observation and earliest recognition of slightest signs of developing toxemia is stressed as crucial.

6. Details of the management of the non-convulsive types are discussed, with emphasis on the necessity of terminating the pregnancy should very prompt amelioration of the syndrome not attend the institution of therapy.

7. The wholly different management of the convulsive types is dealt with.

8. In final briefest summary: a. Purely hypertensive toxemias may be managed with a certain degree of conservative expectancy in the fetal interest, provided the mothers are properly safeguarded by hospitalization, close medical observation and constantly available blood; b. Progressively severe "true" pregnancy toxemias whether engrafted on pre-existing hypertension or not, must not be temporized with. Ruthlessly radical termination of pregnancy serves alike the interest of mother and fetus; c. The convulsive toxemias should be treated wholly along conservative medical lines, without artificial interference with the pregnancy; d. Recovered convulsive toxemias should have the pregnancy terminated exactly as in the severe progressive non-convulsive types.

DISCUSSION

Dr. Nevin S. Scrimshaw: Dr. Cosgrove has indicated the difficulty of distinguishing pre-eclampsia from essential hypertension without adequate previous data on the patient. Even when essential hypertension is known to antedate pregnancy, it is not always easy to decide whether pre-eclampsia is superimposed. Our preliminary work at the University of Rochester with Dr. Eric Alling suggests that electrophoretically determined albumin values of serum or plasma from these women may be of diagnostic aid.

Thirty-one out of 37 pre-eclamptics of varying degrees of severity and 7 out of 7 eclamptics had electrophoretic albumin values of 2.8 gms. per cent or less while only 10 of 40 normal patients studied near term showed albumin values as low as this. This lowering of the albumin value measured by electrophoresis does not seem to depend on the degree of albuminuria. While none of the six uncomplicated hypertensives studied in their last trimester showed values below this figure, the three patients considered to have pre-eclampsia superimposed on their hypertension showed values of 2.08, 2.37, and 2.49 gms. per cent.

The quantitative values of other electrophoretically determined components are variable in these conditions. Although the alpha₂ and beta fractions are commonly elevated in both normal pregnancy and pre-eclampsia, they may yet prove of interest in the latter condition. We have not found an elevated gamma globulin in a pre-eclamptic or eclamptic and this fraction is frequently lower than normal in these conditions. We are now examining the electrophoretic patterns not only for quantitative differences in values but also for qualitative changes in the shape of the peaks.

In summary, we are coming to expect a definite change in electrophoretic pattern in 80 to 90 per cent of our clinically diagnosed pre-eclamptics. However, approximately 25 per cent of normal patients in the last trimester may show a similarly suggestive pattern. We believe that the difference in pattern between essential hypertension alone in late pregnancy and that with superimposed pre-eclampsia is evidence that these two conditions

can be distinguished. Since the distinction is important in the prognosis and handling of such cases, we feel that the electrophoretic technique is of potential value. We are also using it to follow selected hypertensives, nephritics and previous pre-eclamptics through their pregnancy in the hope of securing warning of impending complication by pre-eclampsia.

DR. RUCKER: I have no inclination that way, but I am glad to hear Dr. Cosgrove sanction digitalis.

I approached the subject years ago from the standpoint of what caused patients to die in eclampsia. Of course, first in the point of time was a state of continued convulsions in which the patient died of exhaustion. If they lived through that they frequently developed a pulmonary edema. The cardiologists said it had nothing to do with the heart but nevertheless they drowned with this edema. If they survived they frequently developed a renal less they drowned with this edema. If they survived they frequently developed a renal insufficiency, and if they survived that they then developed infection and died of a pneumonia 10 or 12 days after they got over the toxemia. That was the pattern that most of my patients who died followed. Some of them got well of course, but the ones that died, died in the manner described. So my problem from the therapeutic standpoint was, first, to stop the convulsions; second, to guard against the pulmonary edema, and the third, to guard against anuria, and of course to try to keep them from getting infected.

Magnesium sulfate intravenously was a tremendous help in stopping the convulsions. Some of them did not stop with that. Veratrone, Dr. Cosgrove, has been very helpful in my hands in stopping the ones who did not respond to the magnesium sulfate.

When I was able to see the patients before they developed pulmonary edema and was able to give them a half cat dose of digitalis, none of them developed pulmonary edema.

The ones that I gave enough water by mouth, either through a stomach tube, or after waking them up with magnesium sulfate so they could drink it themselves, did not develop anuria.

So my scheme of treating these cases is very much like Dr. Cosgrove's. I have forgotten at the moment what my statistics were but I think there were 7 maternal deaths in 153 consecutive cases, with therapy directed to just those 4 problems.

DR. TORLAND (Philadelphia): I would like to ask Dr. Cosgrove if he has any urge at all to try to employ spinal taps in controlling the convulsions in eclampsia. There is a group in my town that feel very strongly in favor of it and the rest of us are on the fence. I thought perhaps with his knowledge he might be able to throw some light on the subject.

DR. S. T. GARBER: I should like to make some remarks about the use of veratrum viride which has been used continuously at the Cincinnati General Hospital since 1895 with very good results. The time to institute careful treatment is not after convulsions develop but before. Once treatment has been started with this drug, together with other measures, convulsions should never occur. When a patient comes under our care, woe be to the man under whom convulsions develop. No sedatives are employed except magnesium sulfate.

During the 16 years, 1930 through 1946 inclusive, our maternal mortality from eclampsia per se has been 0.6 per cent; one death in 160 consecutive cases. Two other eclamptic patients died of sepsis some days or weeks following delivery. These 2 were very poorly handled obstetrically and occurred before the advent of chemotherapeutic agents. The total uncorrected maternal mortality for patients who had eclampsia is therefore 1.8 per cent.

DR. COSGROVE: I want to thank all the discussers for their interest in what they have said. I shall be very much interested indeed in watching the extension of the work that Dr. Scrimshaw spoke of, and Dr. Rucker and Dr. Garber who are proponents of the use of veratrum. Apparently Dr. Garber's clinic is one of the foci of veratrum allegiance which has lasted all through the long period of the relative discredit of veratrum in other American clinics. I have watched Dr. Garber's reports in the literature with interest and I assure you with a great feeling of envy in the very excellent results he has attained. I hope that I am not so hide-bound that if in our own experience veratrum proves as satisfactory as it has in yours I will not become just as enthusiastic for it as you are.

Dr. Torland, we have had no experience with the spinal taps. We have not found that mere spinal taps have contributed to the condition of these patients. We employed that experimentally a long time ago and were not convinced of its value. I am very much interested, however, in the work that Hingson has recently done in Memphis with the use of high continuous spinal anesthesia in controlling these situations and that may prove to be a very distinct contribution to our therapeutic armamentarium. I just cannot assess it at this time.

ADJOURNMENT OF CONFERENCE

ANNOUNCEMENT

Copies of this issue in the form of a bound monograph are obtainable at $2.75 per copy from the Williams and Wilkins Company, Guilford and Mt. Royal Avenues, Baltimore 2, Maryland.

ERRATUM

In the article by Peters, Man and Heinemann entitled "Pregnancy and the Thyroid Gland," in the October issue of the Survey, page 648, the first line under "Results" should read Figure 2 instead of Figure 1.

Obstetrics

PHYSIOLOGY OF PREGNANCY, LABOR AND PUERPERIUM

THE HUMAN CONCEPTUS DURING THE FIRST TWO WEEKS OF GESTATION

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Human ova obtained from unruptured follicles can be fertilized in the laboratory and cultured to the 3-cell stage. In this paper the writers report the fertilization of 4 human ova by exposure to human spermatozoa in Ringer-Locke's solution. Two of these ova reached the 2-cell stage, while 2 developed to the 3-cell stage.

In nature, human eggs are probably fertilizable for not more than 12 hours. Spermatozoa are apparently capable of fertilizing the egg for at least 48 hours after ejaculation. The human egg reaches the 8-cell stage in 3 days after ovulation.

The fertilized human egg may have reached the uterus as early as the third day after ovulation. On about the sixth day, as a blastocyst, comprising 3 differentiated tissues, primitive trophoblast, ectoderm and endoderm, it makes contact with and begins ingestion of the maternal endometrium, the newly differentiated syncytial trophoblast at the embryonic pole engrossing some of the superficial epithelium.

When 9 days old, i.e., during the tenth day of development (on about the twenty-fourth day of a twenty-eight day cycle), the conceptus has become almost entirely surrounded by endometrium and is about one-half millimeter in diameter. The embryonic disc, comprising ectoderm and endoderm, is well defined. The amniotic cavity is bounded dorsally by the primitive amnion, the cells of which derive from the adjacent cytotrophoblast. The larger part of the trophoblast consists of syncytium in which have appeared many communicating lacunae. Entrance has already been made by the syncytium into a maternal sinusoid, thus permitting maternal blood to flood the lacunar system.

When 12 days old, the conceptus is almost one millimeter in diameter, the embryo itself is about one-tenth as wide, and lies in a cavity about 5 times bigger than itself. This cavity is filled with fluid in which there is growing a diaphanous lacework of extraembryonic mesoblasts that divide this extraembryonic cavity, or coelom, into numerous chambers, one large and many small. The delicate net

that joins the endoderm and with it surrounds the larger chamber is Heuser's membrane. This is probably the *anlage* of the yolk sac. Surrounding this whole central space in which the embryo lies is the trophoblast, the all essential intermediary between the mother and the baby. This comprises 2 types of trophoblast derived from primitive tissue: the cytotrophoblast that bounds the central cavity and the outer syncytium.

By the fourteenth day, the amniotic sac has covered the ectoderm. The mesoblast has formed many extensions from the cavity into the cytotrophoblastic mass, and has stretched the proportionately diminishing syncytiotrophoblast into a thin covering layer that then lines the lacunae. In these papillary outgrowths, the extraembryonic mesoderm extends to form a supporting structure. Maternal blood fills the lacunar spaces. Endodermal cells have proliferated to form the definitive yolk sac. The conceptus after fixation is from 2 to 3 millimeters in diameter.

By the sixteenth day, branched villi of mature appearance, but without a completed vascular structure, are formed. The primitive streak appears on the ventral surface of the ectoderm.

As of June, 1947, the authors' series of very young embryos, excluding those fertilized in vitro, amounts to 26. Of these, 12, or 47 per cent, are considered abnormal, in either trophoblastic or dermal tissue or in both. Two of the imbedded specimens lack the embryonic disc or inner cell mass. Thus, they all might and some surely would have aborted.

In 122 uteri of proved fertile women, 104 of whom had ovulated and been exposed to pregnancy during the ovulation phase, only 26 conceptuses were found. Assuming that none was missed, this gives a fertility index of only 25 per cent.

Ovulation in these 26 well authenticated cases occurred about the fourteenth day before the expected onset of menstruation. 3 figures.

(Probably the most important contribution of recent years in the field of human embryology has been that made by the authors of this and other previous papers on the same general subject. It emphasizes the value of team work in science since the well-planned search of the authors for very early fertilized eggs was reinforced by all the resources of the Carnegie Institution of Embryology in the study of these early eggs. This study was no doubt made easier by the technics which had been learned in the acquisition and investigation of the fine collection of early monkey eggs discovered through the work of Carl H. Hartman, formerly of the Institute staff. The studies of Rock and Hertig also illustrate the fact that the human female is a readily available experimental animal for the study of many problems of reproductive physiology, in which the use of lower animals has very largely preempted the field.

It is now possible to postulate with reasonable accuracy the hitherto blank period represented by the first ten days or so of the life history of the fertilized ovum. It has not been so many years that the young aristocrat of human eggs was the Miller ovum, something like 10½ days old, and a venerable specimen in the light of our newer knowledge. Most of this has been made possible by the intensive search of the authors for earlier specimens, and it is largely responsible for our knowledge of the events occurring before the 10th day, as set forth briefly in the first four paragraphs of the above abstract.

The possibility of fertilizing the ovum in vitro is of course interesting, and will in time enrich the ribald repertoire of the medical jesters whose jokes and stories rather character-

istically deal with some one or other of the human bodily functions. Probably more important is the new knowledge as to the development of the amnion, concerning which it was formerly possible only to speculate on the basis of work on lower animals. In such embryos as those of Miller, Kleinhans-Grosser and Peters, for example, the early amnion was already well formed.

It is of interest, also, to note that this newer work confirms the ideas which had crystallized through investigations along other lines as to the very limited span of fertilizability of the ovum and also the somewhat longer span of fertilizing potency of the spermatozoon.—Ed.)

that joins the endoderm and with it surrounds the larger chamber is Heuser's membrane. This is probably the *anlage* of the yolk sac. Surrounding this whole central space in which the embryo lies is the trophoblast, the all essential intermediary between the mother and the baby. This comprises 2 types of trophoblast derived from primitive tissue: the cytotrophoblast that bounds the central cavity and the outer syncytium.

By the fourteenth day, the amniotic sac has covered the ectoderm. The mesoblast has formed many extensions from the cavity into the cytotrophoblastic mass, and has stretched the proportionately diminishing syncytiotrophoblast into a thin covering layer that then lines the lacunae. In these papillary outgrowths, the extraembryonic mesoderm extends to form a supporting structure. Maternal blood fills the lacunar spaces. Endodermal cells have proliferated to form the definitive yolk sac. The conceptus after fixation is from 2 to 3 millimeters in diameter.

By the sixteenth day, branched villi of mature appearance, but without a completed vascular structure, are formed. The primitive streak appears on the ventral surface of the ectoderm.

As of June, 1947, the authors' series of very young embryos, excluding those fertilized in vitro, amounts to 26. Of these, 12, or 47 per cent, are considered abnormal, in either trophoblastic or dermal tissue or in both. Two of the imbedded specimens lack the embryonic disc or inner cell mass. Thus, they all might and some surely would have aborted.

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PATHOLOGY OF PREGNANCY

THE GUTERMAN TEST IN THREATENED ABORTION

A REPORT BASED ON 100 CONSECUTIVE CASES

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In a recent paper (Bender, J. Obst. & Gynaec. Brit. Emp., **54**: 783, 1947), experimental work was reviewed which suggested that the administration of progesterone in the treatment of threatened abortion is indicated where there is a natural deficiency of the hormone, but that its use in the absence of progesterone deficiency is not only pointless but possibly increases the chances of the abortion progressing. This is because, as a number of authors have shown, one of the actions of the hormone is to increase the amplitude of uterine contractions. Accordingly, before starting specific therapy in these cases it is desirable to divide them into 2 categories—those accompanied by progesterone deficiency and those not so accompanied. This differentiation can be made by estimating the level of urinary pregnanediol excretion, which level is held to provide a reliable index of progesterone metabolism. The Guterman (pregnanediol excretion) test, although less exact than lengthier methods of pregnanediol assay, has been found eminently suitable for this purpose. Because it is economical and can be completed within 3 hours, it does not involve the use of experimental animals, and a 24-hour specimen of urine is not required, 100 ml. of a first morning specimen being sufficient.

The present paper is based on a review of 100 consecutive cases diagnosed clinically as threatened abortion, including 55 already reported (Bender, J. Obst. & Gynaec. Brit. Emp., **54**: 783, 1947), in which the Guterman test was performed. In 78 cases an Aschheim-Zondek test was carried out on the same urine specimen. The follow-up in each case extended primarily for a limited period of 5 weeks, because the test result was significant of the urinary pregnanediol level at the time of test only. The clinical diagnosis of threatened abortion was not confirmed in all cases; in 94 the patient was or had recently been pregnant, while in 6 the condition from which the patient suffered was subsequently shown to be unassociated with pregnancy. In 7 cases, all true threatened abortion, the test result was vitiated because progesterone had been administered within the 72 hours immediately before the collection of the urine for the test. In these a false positive result could therefore not be excluded. The remaining 93 cases fall naturally into 5 groups according to the final diagnoses and the test results.

Group 1a—True Threatened Abortion. The method of treatment and the outcome in the 42 cases showing no evidence of progesterone deficiency as *reflected*

in the urinary pregnanediol level were: of 11 treated with progesterone 7 aborted and 4 did not abort; of 31 not treated with progesterone 6 aborted and 25 did not abort.

Group 1b—True Threatened Abortion. The figures in the 26 cases with evidence of progesterone deficiency showed that of 14 treated with progesterone 2 aborted and 12 did not abort; and of 12 not treated with progesterone 9 aborted and 3 did not abort.

Group 2—Missed or Complete Abortion. The correct diagnosis in these 19 cases was established by the clinical course and by the results of simultaneously performed Aschheim-Zondek tests. This group shows the value of the simultaneous performance of pregnanediol and gonadotrophin pregnancy tests; in missed and complete abortion both are negative, while in true threatened abortion the gonadotrophin test is positive but the pregnanediol test may be positive or negative.

Group 3—Corpus Luteum Cyst. In these 3 cases the positive tests reflected the increased production of progesterone by corpus luteum cysts. The correct diagnosis was established by clinical examination and by the combination of positive Guterman test with negative Aschheim-Zondek test.

Group 4—Not Pregnant. This group comprised 3 cases in which, as in the previous group, a period of amenorrhea was followed by bleeding. They were cases of pelvic tuberculosis, fibroids at the menopause, and psychogenic amenorrhea.

Since the findings in respect to cases of true threatened abortion are statistically significant, the following conclusions appear permissible: 1. In true threatened abortion 38 per cent of cases are associated with progesterone deficiency and 62 per cent are not. These figures correspond closely with those given by Hain (J. Endocrinol., 3: 10, 1942), who employed the lengthier but more accurate gravimetric method of assay of Venning (J. Biol. Chem., 119: 473, 1937). 2. If progesterone is administered to cases in which there is no evidence of progesterone deficiency 64 per cent abort. If, however, such cases are not treated with progesterone the abortion rate is only 20 per cent. 3. When progesterone is given to patients in whom a low pregnanediol excretion indicates a natural deficiency of progesterone only 14 per cent abort. If, on the other hand, progesterone is withheld in such cases the abortion rate is 75 per cent. 4. If without any attempt at subdivision 100 consecutive cases of threatened abortion are all treated with progesterone, 45 will abort, while if none is given progesterone 41 will abort. The above figures substantiate the clinical impression that when all cases of threatened abortion are given progesterone the overall results are not likely to be any better than those obtained when no patient is so treated. 5. If, however, all cases of threatened abortion are subdivided according to their progesterone need, and progesterone is given only when the pregnanediol excretion is low, only 18 per cent abort and considerable salvage of fetal lives is thus made possible. This subdivision is made possible by a simultaneous Guterman test and Aschheim-Zondek test.

(From a practical viewpoint, the main contention of this paper is that progesterone may actually expedite abortion and therefore should never be given unless the patient, on test-

ing, shows a progesterone deficiency. This is a disquieting admonition and the question arises: Can it be true?

The belief that progesterone inhibits uterine contractility is so widely held that the author's statement in regard to its increasing the amplitude of contractions and hence promoting abortion, may evoke surprise. The original understanding about progesterone was, of course, that it acts as a uterine sedative and it has long been so employed in the treatment of threatened abortion, dysmenorrhea and after-pains. This attitude toward the hormone dates back to a series of experiments by Knaus in 1926 on rabbits which led him to the belief that the corpus luteum, in this species at least, had, in addition to its action upon the endometrium, the function of decreasing spontaneous uterine activity and completely inhibiting its response to pituitrin during the term of the transplantation, implantation and development of the fertilized ova (J. Physiol. *61*: 383, 1926). A host of experiments confirmed these observations and it is still rather generally believed that in the rabbit progesterone does act as a uterine sedative. Even here, however, there are skeptics to be found, such as Bell who has incriminated the technics used in studying uterine motility and believes that the empty rabbit uterus is very active under the influence of progesterone (J. Physiol. *95*: 8 P, 1939).

In 1929 Knaus extended his experiments to the human uterus and found that it resembled that of the rabbit in spontaneous motility and response to pituitrin in the follicular phase and in the inhibition of the latter during the corpus luteum phase. Moreover, he showed that the human uterus during the corpus luteum phase became almost or quite inactive (Zentralbl. f. Gynäk. *53*: 2196, 1929).

Although this work of Knaus was amply confirmed and seemed to be completely established, there began to appear in 1931 a series of papers by various authors which contradicted it. For instance, in that year, Schultze reported experiments resembling those of Knaus but the results and the conclusions he drew therefrom were in sharp disagreement. He found only a slight spontaneous motility and response to pituitary stimulation in the follicular phase, while from about midcycle onward a definite increase occurred in each until within 24 hours of the onset of menstruation. He was the first to point out that the amplitude and form of the contractions were characteristic of the phase of the cycle in which they were recorded and that the response to pituitrin increased progressively toward the end of the cycle and reached a maximum between the 20th day and 24 hours before the onset of the next period (Zentralbl. f. Gynäk. *55*: 3042, 1931). Likewise, in 1934, Moir, using an intrauterine bag, found that the contractions were much stronger in the second half of the cycle and even more forceful during menstruation when they came at 2-minute intervals. Both in the premenstrual phase and the menstrual phase of the cycle pituitrin caused "spasmodic contractions." (Tr. Edinburgh Obst. Soc. *54*: 93, 1934.)

After reviewing this whole problem extensively several years ago, Henry and Brown reached the conclusion on the basis of their own as well as others' work that the spontaneous activity of the human uterus and its sensitivity to pituitrin are greatest in the luteal phase of the cycle and, by the same token, that progesterone is not a uterine sedative (Am. J. Obst. & Gynec. *45*: 927, 1943). This paper of Henry and Brown is a searching analysis of this question, is well documented by meticulous, original work and would seem to disprove rather conclusively the old tenet advanced by Knaus.

Accordingly, there can be no doubt that Bender can document his statements that, in the light of modern knowledge; the action of progesterone on the human myometrium may be directly the reverse of that originally announced. Nevertheless, this is still an unsettled question since some of our leading authorities on uterine physiology, such as Samuel R. M. Reynolds, are very dubious about this alleged stimulating action of progesterone on uterine muscle. With seeming justice Reynolds points out that the technical difficulties are great and that any over-distension of the uterus produced by an experimental balloon might well invalidate any conclusions to be drawn. But quite apart from the difficulty of making deductions from such an artificial set-up as an intrauterine bag (upon which all this work is based), it should be emphasized that no experimental observa-

tions have been made, for obvious reasons, on the reactions of the human pregnant uterus to progesterone. To me it seems a very far cry from the reactions of a nonpregnant uterus with a mechanical bag in situ to a pregnant uterus containing a physiologic product of conception; and while ample experimental evidence in support of Bender's view can be adduced, as reviewed above, I do not find myself able in this moot problem to answer the question posed in the first paragraph of this note in the affirmative. If it is eventually to be answered in the affirmative, several thousand obstetricians have been very wrong about progesterone these many years.

In his original paper Bender is careful to point out that other deficiencies, in addition to progesterone lack, must be looked for and treated. In this connection, it may be well to recall that thyroid deficiency is a much more common cause of abortion than shortage of the corpus luteum hormone,—in a ratio probably of 6 or more to 1.—Ed.)

TWIN PREGNANCY WITH ACUTE HYDRAMNIOS TREATED BY PARACENTESIS UTERI

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Brit. M. J., 2: 205–206, July 24, 1948

Puncture of the uterus through the abdominal wall in an effort to reduce the amount of liquor amnii without terminating pregnancy was first advocated by Schatz (Arch. Gynäk., 19: 332, 1918) and carried out by Henkel (Zbl. Gynäk., 43: 841, 1919) and Wormser (Zbl. Gynäk., 44: 137, 1920). Textbooks of obstetrics hardly mention the method and generally give a poor prognosis for the fetus in acute hydramnios. The procedure was advocated in this country by the late Mr. Carnac Rivett (J. Obst. & Gynaec. Brit. Emp., 40: 522, 1933), who referred to it as "a rational method of treating hydramnios, since in all cases sufficiently acute to demand interference any other line of treatment would result in a miscarriage or the birth of a barely viable child." The author reports the following case of acute hydramnios occurring in a twin pregnancy.

The patient was a multiparous gipsy, age 25, admitted to the hospital on May 18, 1947, on account of acute hydramnios. Her last menstrual period had begun on November 13, 1946, but instead of being 6 months in size the uterus had the dimensions of a full term pregnancy. There was a history of sudden abdominal enlargement with discomfort for the past few days, and of severe abdominal pain during the 24 hours preceding admission. The fetal heart sounds could not be heard, and parts were difficult to identify, although external ballottement was just possible. The patient was in considerable pain, requiring an injection of morphine a few hours after admission. The uterus, though distended, tense, and tender, was not "board-like" as in concealed antepartum hemorrhage, and it was concluded that the excessive uterine enlargement was due to hydramnios. The temperature was normal (and remained so throughout the patient's stay in the hospital) but the pulse rate varied from 90 to 130. Further investigation re-

vealed a hemoglobin of 75 per cent and a negative Wassermann. The patient was Rh-positive and her blood pressure was 115/85. The urine contained a trace of albumin but no casts or blood cells, and was sterile on culture. Radiological examination revealed a twin pregnancy, with the infants probably of no more than 28 weeks' maturity, one presenting by the vertex and the other by the breech. The first paracentesis uteri was performed on the day after admission, when 4 pints 16 oz. of clear liquor amnii was released. A week later the procedure was repeated and 3 pints 2 oz. of liquor was withdrawn. In a 3rd aspiration on June 1st, a further 3 pints 15 oz. was drained, making a total of 11 pints 13 oz. removed in 3 weekly sessions. By this time the patient was very well and fit to be discharged from the hospital. During the remainder of the pregnancy the woman was seen regularly in the antenatal clinic. She remained in good health, and there was no recurrence of the hydramnios. It was, however, noted and confirmed by x-ray that one fetus failed to grow while the other continued to develop normally. Spontaneous delivery of uniovular twins occurred at full term on August 22; the first was a living female weighing 6 lbs., 6 oz., and the second a fetus papyraceus, 12 in. long and weighing 11 oz. There was 1 large placenta, about a third of which was infarcted and had obviously not been functioning for some time. The living infant was perfectly healthy, and her progress as well as her mother's was uneventful, both being discharged from the hospital on September 1st.

Similar cases have been reported by Lloyd (Middlesex Hosp. J., **43**: 5, 1943) and by Erskine (J. Obst. & Gynaec. Brit. Emp., **51**: 549, 1944). It is submitted that by no other method of treatment could a living mature infant have been obtained in the case described. It is uncertain which of the 2 gestation sacs was hydramniotic, but it is tempting to argue that the hydramnios failed to recur because of the death of the fetus in whose bag the liquor had previously accumulated. In some cases there is indeed a recurrence of the hydramnios, and it is this observation which has brought the method of abdominal aspiration into disrepute. There is, however, no objection to repeating the process, providing that x-ray has failed to show a fetal abnormality. If there is a malformation present, surgical induction of labor per vaginam is indicated, and paracentesis uteri can have no place in the management of such a case.

(Our experience with paracentesis for acute hydramnios is limited to 4 cases, all twin pregnancies. In 3, labor ensued within a few hours of the procedure despite the fact that care was taken to withdraw only about ⅓ of the total quantity of fluid present. Paracentesis, therefore, should never be used unless one's hand is forced by the distress of the patient. This usually takes the form of abdominal pain but is occasionally respiratory. The advantages of the method over puncture of the membranes from below are: 1. a certain proportion of patients, but probably a minority, do not go into labor and can be carried nearer term; 2. since only a fraction of the fluid is removed, it is less likely to cause premature separation of the placenta, an accident met occasionally when huge amounts of fluid are released suddenly by puncture of the membranes through the cervix; 3. it is less likely to introduce infection. The disadvantages have to do chiefly with possible perforation of the placenta and whatever sequelae might ensue. No accidents due to placental injury have been reported, however, as far as I know. Provided the patient has never had a previous abdominal operation, the likelihood of injuring intestine in this particular type

of abdomen is nil, I should think. It is my feeling that paracentesis is worthy of trial in those rather rare cases in which further temporizing is out the question and in which release of the fluid in one way or another becomes mandatory. I think that time will show that its advantages outweigh the conceivable dangers, but I am not sure.—Ed.)

SECONDARY ABDOMINAL PREGNANCY WITH SURVIVAL OF THE FOETUS AND MOTHER

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M. J. Australia, 405–407, March 27, 1948

Mrs. M. C. F., a 17 year old white primigravida, was admitted to the Towns ville Hospital on February 20, 1947, her last menstrual period having occurred in June, 1946, complaining of severe pain in the lower part of the abdomen spreading quickly all over the abdomen. On examination her temperature was 99 and the pulse 100. The uterus appeared to be of about 34 weeks' gestation. The fetus was thought to be presenting by the breech and lying on the right side of the uterus. The abdomen, however, was difficult to palpate on account of tenderness and muscular guarding. The pain gradually subsided over the next 12 hours and there was no change over the next 5 days, except that the fetal position converted itself to a transverse lie. On February 25th a vaginal examination was done, the fetal heart having been heard at 130 per minute at the umbilicus. The cervix was small and soft but closed. The uterus could not be felt. Occupying the pelvis and continuous with the abdominal tumor was a tense, cystic mass with the fetus lying above all this. Two diagnoses were entertained: (1) abdominal pregnancy, on account of the easily palpable fetus and of inability to palpate the uterus or uterine contractions; (2) pregnancy complicated by a large ovarian cyst which pressed on the lower part of the uterus and prevented entry of the fetus into the pelvis. The second diagnosis was thought to be the more likely and it was decided to attempt to remove the cyst and perform a cesarean section in the event of trouble.

On February 28th, under "open" ether anesthesia, the abdomen was opened by a midline incision and on opening the peritoneum a large reddish-blue cystic tumor was seen extending to the umbilicus and occupying the pelvis. Above it a loop of umbilical cord was seen. The child was seen lying transversely across the upper part of the abdomen, its head partly enveloped in a piece of ragged amnion, but the rest of its body and limbs mingling with the small intestine, transverse colon and omentum. The 4 pound 2 ounce child was delivered by breech extraction; it was cyanosed but the cord pulsated strongly and in a few minutes it cried. The infant subsequently did well. The abdomen was then examined. The cystic tumor by this time had shrunk to about ⅓ of its original size and was seen to be the placenta contained within the left broad ligament. The uterus was soft,

congested and pushed to the right, and was the size of a 3 months pregnancy. The right fallopian tube and ovary were normal; the left tube was edematous, enlarged and elongated. The left ovary contained the corpus luteum. On examination, the left tube was patent and appeared intact. The left broad ligament, containing the placenta, the left tube, and ovary, was excised en bloc without hemorrhage by clamping the pedicle. The patient made an uneventful recovery. She passed a decidual cast on the 8th day.

Questioning of the mother revealed that she had been seen in another hospital when about 12 weeks pregnant, at which time examination apparently revealed the uterus to be the size of a 12 weeks pregnancy with a small hard lump felt on the right side of the uterus. Five days later, after lifting a weight, the patient experienced severe pain in the left side of the abdomen. However, examination revealed no change in the findings. Further examinations up to 25 weeks apparently revealed a normally progressing pregnancy. The author believes that the small hard lump felt at 12 weeks was the gestation distending the middle of the left fallopian tube and that the episode of pain represented rupture of the ovum into the left broad ligament. He further feels that the onset of pain which brought the patient to his hospital was due to rupture of the amniotic sac with peritoneal irritation. Survival of the fetus in such pregnancies is rare, and in this case in which the correct diagnosis was missed, the child was very fortunate indeed.

PREGNANCY AND KYPHOSCOLIOTIC HEART DISEASE

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Gross thoracic deformity is a relatively infrequent complication of pregnancy. There have been 7 cases of kyphoscoliosis in some 50,000 patients at New York Lying-in Hospital from 1932–1947, or 1 in approximately 7000 obstetrical cases. Two of the 7 cases showed evidence of marked cardiac embarrassment in the course of pregnancy, the vital capacity of 1 reaching a low of 700 cc. at term, and the other 1100 cc. at term. In 1 or another of their pregnancies both of these patients manifested frank heart failure but survived.

The author recalls that the average duration of life in kyphoscoliosis is 30 years. Death is usually due to cardiorespiratory causes. The spinal deformity distorts the thoracic cage so as to encroach upon the space occupied by the heart and lungs. Abdominal and thoracic respiration is obstructed, producing areas of atelectasis and compensatory emphysema. There is an increased tendency to respiratory infection, resulting in pleural adhesions. These pulmonary changes burden the right side of the heart and ultimately the left side as well. Torsion

of the heart and great vessels adds to the cardiac work. Compensatory cardiac hypertrophy is interfered with if generalized hyperplasia exists.

Special cardiac evaluation is indicated if pregnancy is contemplated by the kyphoscoliotic patient. The cardiac status of the kyphoscoliotic patient should be determined prior to or early in pregnancy. Studies should include evaluation of the degree of deformity, cardiac size, vital capacity, electrocardiogram, and cardiac reserve. If the cardiac reserve is significantly limited prior to, or early in, pregnancy, it is certain to become further jeopardized with advanced gestation, and pregnancy is generally contraindicated. Early pregnancy may be interrupted vaginally if indicated. In more advanced pregnancy, significant impairment of the cardiac reserve calls for a strict regime of limited activity, restricted sodium and fluid intake, and avoidance of upper respiratory infection. Anemia should be corrected. Hospital admission and digitalization may become indicated. Should these measures fail, to the extent that cardiac decompensation develops or is imminent, premature delivery must be considered. Kyphoscoliosis also poses a special obstetric problem. The changes in pelvic architecture depend on the site of the lesion. If the kyphoscoliosis is in the upper spine, compensatory lordosis occurs and there is little pelvic change. If the lower lumbar spine is involved, the sacrum is drawn up and out of the pelvis, the promontory is displaced upward and backward, the coccyx forward and inward, the ischia come together, and there is increased pelvic inclination. Here the anthropoid tendency is marked. If the last lumbar or first sacral vertebra is involved, there is roofing of the inlet, resulting in the pelvis obtecta. Although the present series is admittedly too small to warrant any far reaching conclusions according to the author, certain observations are evident. Labor has a definite tendency to be prolonged. The average duration of labor for 5 primigravidas was 30 hours and that for 2 multigravidas was 22 hours in contrast to values of 18 hours and 12 hours, respectively, for the total clinic population. Three of the 7 labors were prolonged beyond 30 hours whereas the incidence of such labor in the total clinic population is only 9 per cent. The tendency to prolong labor may be accounted for partly by the pendulous abdomen and partly by the anthropoid character of the pelvis. Five of the 7 patients showed this type of pelvis, which predisposes to late engagement. The infantile mortality in the present series (based on 8 viable babies) was 12.5 per cent. Accordingly cesarean section should be seriously considered for the safety of the mother if there is serious kyphoscoliotic heart disease, and for the safety of the child if dystocia labor can be predicted.

If vaginal delivery is anticipated the cardiac status should be carefully observed during labor, for the height of the burden may come at this time. The patient should be kept upright in bed and given oxygen throughout labor, delivery and the first 24 hours postpartum. Cardiac strain may be reduced by performing the delivery as soon as feasible after full cervical dilatation, to avoid the bearing down efforts of the second stage of labor. Respiratory depression from analgesia and anesthesia should be avoided. Local anesthesia at the time of delivery will help prevent pulmonary infection which may result from inhalation anesthesia and will decrease the loss of blood. In the event of frank cardiac decompensation with pulmonary edema, atropine, aminophylline, and bloodless tourniquet phle-

botomy are indicated. The prophylactic administration of antibiotics during labor and the early puerperium will aid in preventing infectious complications. Early puerperal ambulation is encouraged.

(The kyphoscoliotic heart is a topic which is long overdue for discussion in the American literature because, with the exception of a chapter in Jensen's book and a section in Hamilton's work, the condition has been almost completely neglected in this country. Yet, cardiac complications are the gravest threat which these patients face. In the 50 fatal cases of kyphoscoliosis associated with pregnancy collected by Jensen, at least 31 were due to heart failure,—far more than were caused by pelvic dystocia (Jensen: The Heart in Pregnancy, The C. V. Mosby Co., St. Louis, Missouri, 1938, p. 333–341).

The incidence of kyphoscoliosis in our clinic has been somewhat higher than in Mendelson's, namely, 9 patients in the last 11,000 deliveries, or 1 in about 1200 cases. Two patients experienced borderline failure and in a third the vital capacity went down to 800 cc., but there were no other signs or symptoms of embarrassment.

In regard to the long labors which these patients sometimes have, faulty alignment of the uterine axis with that of the birth canal is a common cause,—quite apart from strictly pelvic factors. Since the kyphosis tilts the thoracic cage forward and downward, the distance between the xiphoid process and the symphysis may be reduced to 17 or 18 cm. and as a result of this diminution in abdominal capacity, the uterus near term is often pushed forward to an extreme degree,—a "pendulous abdomen," as it were, for which there is no correction.

All in all, the kyphoscoliotic patient is a poor subject for childbearing. If the condition is entirely thoracic, cardiac complications are a threat; if entirely lumbar, midpelvic contraction is common and, if low down, may be extreme; while in the cases in which the gibbus is thoracic-lumbar, both heart and pelvis may be sources of trouble; and in any type of the disease faulty alignment of the uterus with the birth canal may cause uterine inertia. Although Mendelson's 7 patients all survived as did our 9, the maternal mortality in this group as a whole is high and childbearing should be limited.—Ed.)

THE KYPHOSCOLIOTIC HEART IN PREGNANCY AND ITS ELECTROCARDIOGRAM

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The author reports a sudden death near term in a 40 year old primigravida with kyphoscoliosis as the result of heart failure. The patient had shown hypertension of 170/90 at the 7th month and was admitted to the hospital at that time and remained there throughout. With suitable therapy the pressure fell to 140/90, but later rose to 210/120. The hypertension was treated unsuccessfully by vena section. A cardiologist found the heart normal and regarded the prognosis, despite the hypertension, as satisfactory. In the last month of pregnancy the patient developed a mild bronchitis. About 14 days before the calculated date of confinement, she arose at night to go to the bathroom, became acutely short of breath, fell unconscious, and after a few gurgling breaths, died. Immediate postmortem section produced a living child.

Autopsy showed: Severe thoracic kyphoscoliosis, hypertrophy of both the right and the left sides of the heart, extreme edema of the lungs and mucopurulent bronchitis.

In an effort to develop some method by which the cardiac prognosis in such cases could be evaluated, the author had employed the electrocardiograph. In 510 electrocardiographs of normal pregnant women, he found that changes in position (standing, sitting, and recumbent) produced decided alterations in the height of the various waves and their configuration. In several patients with kyphoscoliosis he found no such alterations. He believes that this indicates a positional fixation of the heart in these cases with no possibility of change in the electrical axis, and a corresponding lack of adaptability to positional change as well as to stress and strain. The author emphasizes the fact that this method of cardiographic examination is of little or no prognostic value in the individual case but should prove helpful in revealing whether a patient has a so-called kyphoscoliotic heart, that is, one which is held tightly in position by the pressure of surrounding tissues.

(The many hazards faced by the kyphoscoliotic gravida are emphasized in the preceding abstract of Mendelson's article and the appended editorial note. When a severe degree of hypertension is superimposed on these, as it was in Mestwerdt's patient, the gravity of the situation is apparent. Moreover, his patient was 40 years old. In the kyphoscoliotic heart as in other cardiac disease, the outlook becomes worse with advancing years, a point that Jensen has particularly emphasized.

The outlook in this case was so very bad that the result would probably have been the same regardless of the management. On hindsight, however, the month-long history of mild bronchitis would seem significant. In this connection it is informative to note that this same history of bronchitis leading up to pulmonary edema and death occurred several times in Jensen's 50 fatalities associated with kyphoscoliosis in pregnancy. The important thing here is simply to be aware of the cardiac hazard which these women face in pregnancy and then a "mild bronchitis" will not be neglected,—especially in a 40 year old primigravida with a pressure of 210/120.

The exact mechanism by which kyphoscoliosis conduces to heart failure seems to be an unsettled question. Although Mestwerdt may be correct in assigning it to positional fixation of the heart by the pressure of surrounding organs, other students of the subject express a different opinion, notably Chapman, Dill and Graybiel (Med., 18: 167–202, 1939). They believe that the primary effect is on the lung tissue with consequent embarrassment of the heart. In an intensive study of 5 patients with thoracic kyphoscoliosis they found that one of the striking features in the measurements of lung volume was the absolute and relative reduction in vital capacity. The values for the vital capacity ranged from 700 to 2520 cc. which represent a decrease of about one-half the normal value. Furthermore the vital capacity constituted from 35 to 53 per cent of the total lung volume in these patients, while in the normals studied it amounted to 57 to 69 per cent of the total. The averages were 44 and 63, respectively. The ratio of residual air to vital capacity was 1.3 in the kyphoscoliotic patients and 0.6 in the normal subjects; this best explains the respiratory difficulty and habitual dyspnea which these patients suffer. Additional evidence that the chief effect in this syndrome is on the lungs is found in the clinical fact that pulmonary infection, respiratory depressants or any process that further reduces pulmonary function in the hunchback may lead to pulmonocardiac failure and even death. In these deformed people the usual mechanism of respiration is altered by the great limitation of costal movement. The ribs move only ineffectively and breathing is accomplished largely by movements of the diaphragm. Partial collapse and infection are but natural results in these poorly aerated lungs. Chapman, Dill and Graybiel believe that the hypertrophy

and ultimate failure of the right ventricle which are observed in these patients result from the increased work and pressure which have to be maintained by the right ventricle in order to support arterial oxygenation through the cramped and undeveloped lungs.—Ed.)

PERNICIOUS ANAEMIA OF PREGNANCY AND THE PUERPERIUM

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Addisonian pernicious anemia is an uncommon disease but pernicious anemia of pregnancy is much rarer still.   The literature dealing with pernicious anemia of pregnancy has been fully reviewed by Callender (Quart. J. Med., **13**: 75, 1944) who described 25 cases which she observed personally.   Davidson, Davis and Innes (Brit. M. J., **2**: 31, 1942) have described 16 cases.   Of 521 cases of macrocytic anemia examined by the authors during the past 7 years only 31 were associated with pregnancy, and of these only 4 have been seen since the introduction of folic acid.   In the American literature, 3 cases have been described by Spies (J. A. M. A., **130**: 474, 1946) and one by Moore et al (J. Lab. clin. Med., **30**: 1056, 1945).   Davidson and Davis (Advances in Internal Medicine 2: 481, New York, 1947) have drawn attention to 4 points of particular importance in relation to the pernicious anemia of pregnancy.   (1) The diagnosis of pernicious anemia of pregnancy depends essentially on the demonstration of typical megaloblasts in the bone marrow, since the peripheral blood picture may be quite unlike that of Addisonian pernicious anemia, the color index may be below unity, and the M.C.V. within normal limits.   (2) Although free hydrochloric acid is often present in the gastric juice, in a number of cases a histamine-fast achlorhydria is found.   In such cases it may be difficult or impossible to decide whether the case should be classified as pernicious anemia of pregnancy or Addisonian pernicious anemia complicated by pregnancy unless the effect of stopping all forms of liver therapy is observed for a period lasting up to 2 years.   (3) The response to parenteral liver therapy may be normal, poor and delayed, or absent.   (4) Cases refractory to parenteral liver therapy will respond promptly to oral treatment with proteolyzed liver or to cooked liver (Fullerton, Brit. M. J., **1**: 158, 1943).

No satisfactory explanation is as yet available of the mechanism underlying the development of a megaloblastic anemia in pregnant women.   The anemia could develop as a result of defective intake of some factor necessary for normal blood formation, from a failure in the production of Castle's intrinsic factor, or from a defect in absorption from the alimentary tract.   The authors have seen a case diagnosed as pernicious anemia of pregnancy and 2 cases diagnosed as idiopathic refractory megaloblastic anemia which were subsequently shown to be cases of idiopathic steatorrhea.

The authors present 3 cases of pernicious anemia of pregnancy and 1 case of

Addisonian pernicious anemia complicated by pregnancy which responded excellently to treatment with folic acid.   Three of the cases had failed to respond to the parenteral injection of liver extracts prior to the administration of folic acid.   It was felt that many cases of pernicious anemia of pregnancy are suffering from a dual deficiency of iron and the factor required for maintenance of normoblastic blood formation and that it is therefore desirable that both deficiencies be corrected simultaneously.   However, in the 4 patients reported, iron was deliberately withheld during treatment with folic acid in order to simplify the interpretation of the therapeutic response.   The authors conclude from their investigation that folic acid would seem to be the best agent available at the present time for the treatment of pernicious anemia of pregnancy because it can be administered orally in the form of a small tasteless tablet and because of the rapid clinical and hematological improvement which results even in cases refractory to parenteral liver therapy.   Furthermore, since the duration of treatment with folic acid is limited to a few weeks, the danger of producing subacute combined degeneration of the spinal cord is greatly reduced as compared with Addisonian pernicious anemia.   They believe, however, that further time must elapse before it can be stated confidently that neurological features will not occur in patients with pernicious anemia of pregnancy receiving folic acid.

(This article calls to mind the important diagnostic fact that it is not necessary to have an increased corpuscular volume of the red cells in order to make a diagnosis of pernicious anemia of pregnancy, despite the fact that the latter is often referred to as "a macrocytic anemia." The fact that megaloblastosis of the marrow is not only an important diagnostic sign of pernicious anemia of pregnancy but is seen also in sprue, is in keeping with the viewpoint that this disease is nutritional in etiology, in the first instance resulting from faulty dietary intake and in the latter from defective absorption from the alimentary tract. Moreover, in India where this type of anemia is so prevalent, the general consensus among obstetricians indicates a nutritional origin. Although the pernicious anemia of pregnancy is uncommon in this country, the few cases I have seen recently responded very well to folic acid and, as the authors say, this agent would appear to be the best available medium for the treatment of this condition.—Ed.)

MEGALOBLASTIC ANEMIA OF PREGNANCY

REPORT OF AN UNUSUAL CASE

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The authors present an unusual case of megaloblastic anemia of pregnancy with associated leucopenia.   The patient was a 21 year old primipara delivered on November 25, 1946, of a healthy female infant at an L.C.C. Hospital.   There

was a secondary degree primary tear which was sutured. The antenatal history was negative, except that the patient was pale throughout pregnancy and had a persistent cough. She became pyrexial on November 26th; sulfadiazine and penicillin were given, but pyrexia continued. The total dose of sulfadiazine was 8 Gms. The hemoglobin on the 27th was 41 per cent. She was transferred to the Northwestern Hospital puerperal sepsis unit on November 29th. On admission she was very pale, and had a septic second degree tear of the perineum, with a septic and lacerated cervix, but a normally involuting uterus. The spleen was palpable. Cultures from the cervix yielded no significant growth, and urine and blood cultures were sterile. A blood count showed marked anemia, the hemoglobin being 35 per cent, the red count 1,790,000, and the white blood count 5,000. The differential count was 37% neutrophils, 36% lymphocytes and 27% myeloblasts. She was accordingly transfused slowly with 1 liter of blood. The blood count, however, showed no improvement after the transfusion. Sternal puncture was performed on December 3rd. In spite of penicillin treatment pyrexia persisted and numerous small pustules developed on the wrists and arms. Later, retinal hemorrhages occurred. Intensive liver treatment was started on December 13th and a further blood transfusion was given with but little effect. The patient died suddenly on December 31st.

The postmortem findings were as follows: caseous tuberculosis of the hilar glands and a caseous tuberculous focus, 1 cm. in diameter, in the lower lobe of the right lung. The heart muscle was thin, pale and flabby, with a few subpericardial hemorrhages. The spleen weighed 450 grams and was congested and friable. The liver weighed 3000 grams and was pale and rather greasy. The uterus showed some necrosis of the placental site but was well involuted. Apart from generalized pallor there was little of pathological importance in the other organs. The bone marrow of the sternum, ribs, and femur was a rich dark red color. Sections and films of sternal marrow showed an extreme cellularity, the predominant cell being of the primitive hemocytoblast variety with large numbers of megaloblasts (mostly early) and normoblasts. Granulocytes and their precursors were almost completely absent. The white blood count prior to death had been 1500.

In the various reports of cases already in the literature, little mention is made of any changes in the white blood cells. Callender (Quart. J. Med., 13: 75, 1944) found a leucopenia common with "myelocytes and young forms." Other writers record low total white blood cells but give no differential counts. The authors have been unable to find any reference to such profound immaturity of the white blood cells in the peripheral blood in any other cases of megaloblastic anemia of pregnancy, although myeloblasts are occasionally found in the peripheral blood in pernicious anemia. In the authors' patient the leucopenia was constant and the white blood cells decreased gradually from 5000 to 1500 per cmm. the day before death. Myelocytes, promyelocytes, and myeloblasts formed from about 20 to 50 per cent of the total for the first 2 weeks, gradually falling with the count. The question of agranulocytosis following sulfadiazine was raised after the first count. In the experience of the authors, however, it is

unusual to find early granulocytes in the peripheral blood in agranulocytosis except during recovery. Generally the polymorphs drop suddenly without warning, and no precursors reach the peripheral blood until regeneration of the marrow is taking place. Furthermore, this patient had received only 8 grams of sulfadiazine. The alternative suggestion of acute leukemia appeared at first to fit the severe anemia with myeloblasts in the peripheral blood, but sternal puncture did not confirm this. The findings of a definite megaloblastic reaction in the marrow suggested rather a deficiency of the hemopoietic principle, and it seemed probable that this was the primary abnormality and that the high proportion of myeloblasts was due to a coincident failure of maturation of the granulocytes rather than a true leukemic change. Although liver therapy was not begun until a late stage in the disease, the poor response to the 3 preparations used seems to indicate the refractory nature of the anemia. Defective absorption from the intestine may have been partly responsible for producing the anemia. Nutritional deficiency might also account for the failure in maturation of the granulocytes.

(The fatal outcome in this case, the refractoriness of the anemia to liver therapy, the persistent pyrexia and the megaloblastic bone marrow are characteristic of pernicious anemia of pregnancy as it is seen in India. Wills and Mehta, in a study of 50 Indian cases, found that the total leucocyte count ranged between 2700 and 16,600, with an average of 7000 (Indian J.M. Research, 17: 777, 1929-30). In some of these cases, accordingly, a leucopenia does occur and it is conceivable, in exceptional instances, that it might go as low as 1500 on the basis explained by the authors.—Ed.)

PEPTIC ULCER DURING PREGNANCY

WITH A REPORT OF A CASE OF PERFORATION

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Brit. M. J., 74–75, July 10, 1948

Although complaints of indigestion are common among expectant mothers, the association of peptic ulcer with pregnancy is believed to be most unusual. During the period 1928–37 Sandweiss et al (Am. J. Obst. & Gynec., 45: 131, 1943) discovered only 1 case of proved duodenal ulcer in 70,310 pregnancies collected from 5 hospitals in Detroit. Over a similar period in New York City 1 case of gastric ulcer was reported from 348,310 pregnancies. Both cases resulted in death from perforation. Avery Jones (Brit. M. J., 2: 479, 1947) stated that no case of proved peptic ulcer was discovered among 10,000 pregnancies at the antenatal clinic of the Central Middlesex Hospital even in the few cases referred to the dietetic clinic for indigestion.

The following case, in which perforation of a duodenal ulcer occurred at the 36th week of pregnancy, is reported partly because it is so rare and partly because it affords an opportunity of reviewing the effects of pregnancy upon peptic ulcer in general.

A primipara, aged 24, at the 36th week of pregnancy, was admitted to the North Herts and South Beds Hospital on August 20, 1947, complaining of acute abdominal pain.   Four years previously she had been treated in the hospital for a duodenal ulcer, and this had been confirmed by an x-ray.   She had not suffered from any other illness, and did not show any signs of masculine endocrine characteristics.   During her pregnancy she had had 2 severe attacks of indigestion, relieved by alkalis.   A 3rd attack began a few days before admission, and she finally collapsed with a very severe pain in the epigastrium.   When first seen, 8 hours after the onset of the acute pain, she complained of continuous pain all over the abdomen and had vomited twice.   Her temperature was 100 and her pulse rate 84.   The size of the uterus corresponded with the dates, and it contained a live fetus presenting by the vertex.   There were no signs of toxemia but generalized abdominal tenderness and some rigidity were present in the right side of the epigastrium.   No peristalsis could be heard.   Having excluded the possible causes of pain due to the pregnancy, the diagnosis appeared to rest between a perforated duodenal ulcer and a perforated appendix displaced upwards by the enlarged uterus.

Laparotomy was performed 10 hours after the onset of the acute pain.   A high paramedian incision was made and free fluid was encountered.   A small perforation about 4 mm. in diameter was found on the anterior surface of the duodenum. This was closed and a small portion of omentum sutured over it.   A brief search for the appendix served only to show the extreme difficulty of locating this organ late in pregnancy, and in order not to disturb the uterus, the surface of which was already red and injected, the attempt was abandoned.   The abdomen was then closed without drainage.   Morphine and progesterone were given daily in an attempt to postpone labor, but 4 days after the operation labor started, and she was delivered spontaneously of a living child weighing 6 lbs., after an easy labor lasting 17 hours.   Her subsequent progress was uneventful.   A test meal in the puerperium revealed marked hyperchlorhydria, and a barium meal six weeks after the operation showed that the ulcer was still active and there was some delay in emptying.   The diagnosis in this case was not difficult once it was realized that an ulcer had existed before pregnancy.

The reason for the apparently beneficial effect of pregnancy upon peptic ulcer is not altogether clear.   Hurst and Stewart (Oxford Med. Pub., London, 1929), however, describe the rising uterus supporting the stomach as one of the main reasons for the favorable influence of pregnancy upon the symptoms of ulcer. While the support of the uterus might benefit a gastric ulcer in the long type of stomach, it is difficult to see how it could help a duodenal ulcer in the short high stomach.   Two other factors are probably involved: (1) the physiological atony which is believed to occur in the smooth muscle of the alimentary canal during pregnancy; (2) the hypochlorhydria which is so often found during preg-

nancy. On the other hand, it is well known that 80–90 per cent of all peptic ulcers in adults occur in men. Differences in mode of living may be partly responsible, but endocrine factors are probably also involved in this very definite sex-incidence. Way (Brit. M. J., 2: 182, 1945) has suggested that the secretion of acid in the stomach varies inversely with the concentration of gonadotrophic hormone present at the same time in the urine. Bockus (Gastroenterology, 1: 491, 1944, Philadelphia) has suggested a direct relation between pituitary hormones and peptic ulcer apart from pregnancy. He quotes the following evidence as suggestive, but it is still unproved: (1) Pituitary hormones and urinary extracts have prevented experimental ulcer in animals; (2) the occasional occurrence of polyuria in ulcer patients; (3) many female patients with peptic ulcer show masculine endocrine characteristics.

In actual practice the obstetrician faced with the rare association of peptic ulcer and pregnancy need only remember 2 things; first, to survey the case from the endocrine point of view to exclude masculine characteristics suggesting an android pelvis and possible dystocia; and, secondly, to pay serious attention to any symptoms of indigestion that may occur during the pregnancy.

(Gastroenterologists tell me that they wish all their ulcer patients could be in a chronic state of pregnancy because women with ulcers almost always improve decidedly during pregnancy. I have always attributed this to the tendency towards hypochlorhydria which gravidae frequently exhibit but some of the other explanations cited by the author may also play a role.—Ed.)

PREGNANCY AND MULTIPLE SCLEROSIS

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Much has been written on multiple sclerosis, and the literature has been well reviewed by Peckham (N. Y. State J. Med., 45: 618, 1945). However, little has been reported of the effect of multiple sclerosis on pregnancy, labor and the puerperium.

Since 1939, 5 cases of multiple sclerosis associated with pregnancy have been seen at University. The first woman, delivered in 1939, had been observed first 2 years previously because of difficulty in walking, with weakness in both ankles. There was a history of one abortion. Following an essentially negative prenatal period the patient delivered a full-term living child. Postpartum course was uneventful. The multiple sclerosis was not aggravated by her pregnancy, no exacerbation followed, and by 1946 her condition remained unchanged except for some increase in general weakness.

The original complaint of the second patient was also difficulty in walking.

First seen in 1940, she was in no worse condition when she came for prenatal care in 1945–1946. She delivered a full-term child after an essentially normal prenatal course, with normal puerperium and no exacerbation of the multiple sclerosis. A year later condition was quite satisfactory except for a tendency to drag the left leg a little, not noticeable before.

The third patient came in with a strong recommendation from the referring physician for interruption of pregnancy. There was a history of temporary blindness following previous pregnancies and deliveries, in the right eye after the first pregnancy in 1931, left eye after the second, and right again after the third. In this 4th pregnancy, in 1943, following a 1942 episode of left eye blindness, weakness and numbness of both legs and inability to walk without falling, therapeutic abortion and sterilization were done. Her hospital course was uneventful. She has not been seen since discharge.

The 4th patient was admitted in 1946 with a history of multiple sclerosis of 12 years' duration. She had had a therapeutic abortion in 1941. Since neither pregnancy seemed to aggravate the multiple sclerosis, it was felt that this second pregnancy should continue. However, the patient was hospitalized and aborted elsewhere a month later.

The last patient was seen in her first trimester of pregnancy. First medical attention for symptoms of multiple sclerosis had been sought 14 months previously. Pregnancy, labor and postpartum course were uneventful. Delivery and routine Pomeroy sterilization were both done under spinal anesthesia. Her multiple sclerosis was not aggravated by her pregnancy.

These cases seem to indicate that while multiple sclerosis is progressive and remissions and exacerbations normally occur, pregnancy does not accelerate the progress nor cause exacerbations. Multiple sclerosis apparently has no ill effects upon pregnancy or offspring. On the other hand, any woman with a condition as serious and hopeless as multiple sclerosis appears to be at present is probably better off if not burdened with a home and a family. She might well be advised to remain single; otherwise, contraceptives might perhaps be prescribed.

PATHOLOGY OF LABOR AND PUERPERIUM

THE USE OF POST-PITUITARY EXTRACT IN PHYSIOLOGICAL AMOUNTS IN OBSTETRICS

A PRELIMINARY REPORT

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Brit. M. J., 123–127, July 17, 1948

Blair Bell was the first to use post-pituitary extract in obstetric practice, and in 1909 (British M. J., 2: 1490, 1609, 1909) he reported its efficacy in the treatment of postpartum hemorrhage and intestinal atony. Two years later Hofbauer (Zbl. Gynäk., 35: 137, 1911) suggested its use in the treatment of uterine inertia. In 1927 Bourne and Burn (J. Obst. & Gynaec. Brit. Emp., 34: 249, 1927) concluded "that valuable application of a dose of 2 units can be made in cases in which labour is prolonged owing to sluggish pains provided that in primiparae dilatation is nearing completion." There is still, however, a widespread fear, based on unfortunate happenings, of using post-pituitary extracts until labor is completed. Recently Reid (Am. J. Obst. & Gynec., 52: 719, 1946) and Eastman (Am. J. Obst. & Gynec., 53: 432, 1947) have advocated the use of small amounts of post-pituitary extract in cases of prolonged labor. Reid advocates starting with 1 minim and increasing the dosage to not more than 5 minims, whereas Eastman is more cautious and starts with ½ minim and never gives more than 1 minim. Both authors consider it wise to confine this method of treatment to obstetrically normal primigravidae whose progress in labor is tedious.

The authors have addressed themselves to 2 main problems: (1) the induction of labor, and (2) the stimulation of uterine pains in cases of uterine inertia. Their procedure is as follows: Either 9 or 19 ml. of 5 per cent glucose-saline is placed in a small sterile bowl, and to it 1 ml. of pituitrin is added and stirred. The requisite amount of this mixture is then added to a standard bottle containing 500 ml. of 5 per cent glucose-saline solution prepared for intravenous injection. The authors used dilutions of the pituitrin drip of 1 in 2500, 1 in 5000 and 1 in 10,000. By trial they have concluded that 1 in 5000 and 1 in 10,000 solution are preferable, since they seldom cause irregularity of the fetal heart or too intense uterine contractions. In addition to the pituitrin they have sometimes added quinine bihydrochloride 2 gr., carbachol 25 mg., and 100–200 mg. of pethidine to the bottle of glucose-saline. The drip is set up in the ordinary manner, using a vein in either the arm or leg, and the infusion is begun at a standard rate of 40 drops to the minute. This rate is decreased if the pains become too strong or too frequent, and is occasionally increased. Not more than 3 bottles are given on any one day, but the drip is often discontinued and restarted on the following day.

The authors had hoped that the pituitrin drip might offer a safe, efficient, and

reasonably rapid method of inducing labor at any time during the last 3 weeks of pregnancy. They have found unfortunately that, so far, the pituitrin drip, even when quinine and carbachol are added, has proved a quite unreliable method of terminating pregnancy, and failed more often than it has succeeded. They have therefore devised a composite routine for this purpose. To begin with, 4 doses of quinine sulfate 10 gr. are given at 4-hourly intervals. Two ounces of castor oil are given either just before or just after the 3rd dose of quinine. A copious warm enema is administered approximately 4 hours after the castor oil. If the woman does not go into labor within 24 hours from the time that the quinine induction is completed, the membranes are ruptured at a point immediately below the presenting part. Should she not go into labor during the next 24 hours the pituitrin drip is started.

During the first 3 months of 1948, 43 patients were subjected to this method of induction of labor. Twenty-two went into labor within 24 hours of the completion of the quinine therapy; the membranes had to be ruptured in 20 cases; and the pituitrin drip was administered in 9 cases. In 1 of these the pituitrin drip was given 24 hours after the completion of the quinine therapy. The membranes of this patient were not ruptured because she showed a marked degree of pelvic contraction. All the infants, save 1, a breech delivery, were born alive and survived. Only 2 patients caused anxiety, and they were both elderly obese multigravidae. Subsequent labor was in each case associated with marked uterine inertia. One was a 5-gravida, age 35, with hypertension, who had not been pregnant for some years and was overdue; the other was a 6-gravida, age 45, whose first pregnancy had terminated by cesarean section and whose youngest child was 6 years old. In each case delivery was effected by a difficult forceps extraction. The infant of the former patient died as the result of cerebral hemorrhage.

A number of patients were admitted after spontaneous rupture of the membranes. In these cases a pituitrin drip, containing in addition quinine hydrochloride 2 gr. in each bottle of glucose-saline, is set up. The drip is taken down after 2 or 3 bottles have been administered and recommenced the next day. Whereas the drip may have no apparent effect on the first day, it usually happens that uterine contractions occur within 1 to 10 minutes of restarting the drip on the following day.

It is the authors' practice to rupture the membranes when possible in the treatment of placenta previa and to apply a tight binder. In 3 recent cases labor did not supervene within the course of the next 20 hours, so the pituitrin-quinine drip was begun. In 1 case labor pains started almost immediately, while in the other 2 it had to be repeated next day. All these babies were born alive and well.

The authors first treated cases of uterine inertia by the pituitrin drip method in June, 1947, and propose to report the results obtained in 20 consecutive cases treated during the last 5 months. Only 1 of these patients had previously given birth to a full-term living child per vias naturales, and she was a 5-gravida. Two had previously been delivered by cesarean section, and 1 had had 2 miscarriages and a premature infant which had died. Of the 20 patients 4 were 40 years or over and 9 were over 30 years (3 being 38 years old). In 9 cases the head was free

above the brim, and in only 4 was the head fully engaged. One was a breech presentation. After "trial labors" 2 were delivered by cesarean section. Nine patients were delivered by the forceps, and the remaining 9 delivered themselves spontaneously. One baby died from a tentorial tear. The largest infant weighed 9 lb. and the average weight was 7 lb. 6 oz.

The pituitrin-drip does not cause a woman suffering from uterine inertia to have very strong pains, but it does in almost every case increase both the frequency and the intensity of the pains. An elderly primigravida may be in labor for 3 days and longer without any advance of the presenting part and without any dilatation of the external os. The pains, although ineffective, suffice to exhaust her. Morphine and other drugs potent enough to afford the woman adequate rest tend to put her "out of labor." The pituitrin drip is invaluable in such cases and makes possible the use of morphine and pethidine, for the drip can be continued while the patient is adequately narcotized. If the authors had to choose between the narcotic drugs and the pituitrin drip they would unhesitatingly choose the former, but they believe the drip to be a very valuable aid in the treatment of these peculiarly difficult cases. The authors have made a mathematical calculation of the concentration of the oxytocic principle in the blood plasma required to initiate or to stimulate uterine pains. This is partially based on a statement by Kamm et al (J. Amer. chem. Soc., 50: 573, 1928) that they had prepared post-pituitary extracts having an oxytocic activity 150 times greater than that of the standard powder. The authors, therefore, make their calculation as follows. Let it be assumed (a) that the post-pituitary gland elaborates an oxytocic principle at least 150 times more potent than that of the standard powder; (b) that the average pregnant woman possesses 3 liters of blood plasma; (c) that none of the oxytocic activity becomes adsorbed to the red blood corpuscles; and (d) that labor pains do not start until after the drip has been running for 5 minutes, during which time 200/17 or 12 ml. of the drip has entered the blood stream; it would then follow that a concentration of the oxytocic principle in the blood plasma not exceeding 1 in $10,000/12 \times 3,000 \times 150 = 1:375 \times 10^6$ may suffice to initiate or stimulate uterine pains.

The uterus apparently relaxes completely between the pains stimulated by the pituitrin drip. Slight irregularities in the fetal heart were noted occasionally, particularly when the 1 to 2500 pituitrin drip was used. In such cases the drip was slowed. No prominent adverse effects on the fetus were observed. The authors therefore consider it perfectly safe to use the pituitrin drip in cases of contracted pelvis when the head is not engaged, in cases of hypertension, and in cases of placenta previa. They no longer consider it safe, however, to allow patients previously delivered by classical cesarean section to undergo trial labor, and for this reason regard it as unsafe to administer the pituitrin drip to such cases. They feel that the pituitrin drip may be used in all cases in which it is considered desirable and safe to stimulate the uterine pains, and that it is immaterial whether the woman is a primigravida or a multigravida, whether or not she suffers from hypertension, or whether the head is above the brim. They do consider, however, that since pituitrin does cause a higher and more prolonged rise

reasonably rapid method of inducing labor at any time during the last 3 weeks of pregnancy. They have found unfortunately that, so far, the pituitrin drip, even when quinine and carbachol are added, has proved a quite unreliable method of terminating pregnancy, and failed more often than it has succeeded. They have therefore devised a composite routine for this purpose. To begin with, 4 doses of quinine sulfate 10 gr. are given at 4-hourly intervals. Two ounces of castor oil are given either just before or just after the 3rd dose of quinine. A copious warm enema is administered approximately 4 hours after the castor oil. If the woman does not go into labor within 24 hours from the time that the quinine induction is completed, the membranes are ruptured at a point immediately below the presenting part. Should she not go into labor during the next 24 hours the pituitrin drip is started.

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A number of patients were admitted after spontaneous rupture of the membranes. In these cases a pituitrin drip, containing in addition quinine hydrochloride 2 gr. in each bottle of glucose-saline, is set up. The drip is taken down after 2 or 3 bottles have been administered and recommenced the next day. Whereas the drip may have no apparent effect on the first day, it usually happens that uterine contractions occur within 1 to 10 minutes of restarting the drip on the following day.

It is the authors' practice to rupture the membranes when possible in the treatment of placenta previa and to apply a tight binder. In 3 recent cases labor did not supervene within the course of the next 20 hours, so the pituitrin-quinine drip was begun. In 1 case labor pains started almost immediately, while in the other 2 it had to be repeated next day. All these babies were born alive and well.

The authors first treated cases of uterine inertia by the pituitrin drip method in June, 1947, and propose to report the results obtained in 20 consecutive cases treated during the last 5 months. Only 1 of these patients had previously given birth to a full-term living child per vias naturales, and she was a 5-gravida. Two had previously been delivered by cesarean section, and 1 had had 2 miscarriages and a premature infant which had died. Of the 20 patients 4 were 40 years or over and 9 were over 30 years (3 being 38 years old). In 9 cases the head was free

THE NEWBORN

A PRELIMINARY REPORT ON HYDROCEPHALUS, SPINA BIFIDA AND OTHER CONGENITAL ANOMALIES IN THE RAT PRODUCED BY TRYPAN BLUE

THE SIGNIFICANCE OF THESE RESULTS IN THE INTERPRETATION OF CONGENITAL MALFORMATIONS FOLLOWING MATERNAL RUBELLA

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With the assistance of ISOBEL SPENCE

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The complex mechanism permitting normal development and the derangements thereof which lead to congenital malformations are usually considered to be of academic interest, the concern mainly of the experimental embryologist searching for an understanding of the causal network of development. It is only when a disease reaches epidemic proportions and maims hundreds of children, that sufficient public interest can be aroused for a fleeting moment at least to support vital investigations concerned with the influence of maternal metabolism on the welfare of the embryo and infant. This was particularly well demonstrated by the German measles epidemic in Australia where over 200 malformed infants were born to mothers who contracted rubella in the early months of pregnancy.

The diversity of factors which, on occasion, can evoke defects in the offspring of man and other mammals has been examined in 2 reviews (Warkany, J. Vitamins and Hormones, p. 73, Academic Press, New York, 1945; Idem, Advances in Pediatrics, p. 1, Interscience Publishers, London, 1947). The present authors' interest in this problem was aroused during their investigation into the consequences of chronic malnutrition among the Africans. They obtained sufficient evidence to show that malnutrition could derange menstrual rhythm in women, that it was in some way causally related to the high incidence of sterility, abortions, and to the low birth rate of African infants, and perhaps that the high infantile mortality was the consequence not only of the ignorance of African mothers' methods of infant feeding, but also of their poor nutritional status during pregnancy and the enfeebled state of the infant at birth. While subscribing to the view that malnutrition can directly injure the tissue demanding essential nutriments for integrity, their analysis of the pathogenesis of cytosiderosis led them to propound the hypothesis that, apart from interfering with the vitality of essential organs, chronic malnutrition could be complicated by the steady flooding of the circulation with the particles derived from the abnormal metabolism or from the increased permeability of the gut, one of the consequences of

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in the blood pressure of patients suffering from "preeclamptic toxemia" than it does in normal pregnant women, it would be more logical to use pitocin drip in such cases in which patients have hypertension.   They propose in a subsequent paper to discuss this matter more fully, to record the antidiuretic effects of pituitrin, and to reproduce kymographic tracings of the uterine contractions caused by the pituitrin drip.

(It seems strange that someone did not think long ago of administering pituitary extract by the intravenous drip technique.   Other methods directed at moderating the action of this drug, such as nasal applications, thymophysin, the various preparations of pituitrin in oil and pitsulfonate, have been recommended, but it would seem obvious that the intravenous drip technique offers, theoretically at least, definite advantages.   It not only makes it possible to increase by infinitesimal amounts the concentration of pituitary extract in the blood and tissues as desired but also ensures the maintenance at all times of a fairly constant level.   We finally hit upon the idea about 2 years ago and have practically abandoned intramuscular pituitary extract in favor of it.   We adjust the concentration in glucose in such a manner that the quantity of pituitary extract administered over a 30-minute period is approximately $\frac{1}{2}$ minim.   Among other advantages may be mentioned, paradoxically enough, the fact that it is somewhat more difficult and time consuming to prepare and administer and it does not lend itself conveniently to home obstetrics.   If with the cooperation of pharmaceutical firms it could be emphasized that this is the only correct way of giving pituitary extract in the first and second stages of labor, it might help reduce the injudicious use of the drug in the home and its haphazard and "spur of the moment" employment in hospitals.

Although the authors are to be congratulated on presenting this new and valuable technique to the profession, I disagree vehemently with their recommendation of pituitary extract in the presence of pelvic contraction.   Uterine inertia is a common accompaniment of labor with contraction of the pelvis and its degree is more or less in proportion to the futility of the outlook.   In many of these borderline pelves strong pains would doubtless force the baby through but I am certain that any widespread attempt to do this by pituitary extract will result in many injured babies and not a few ruptured uteri.   The uterine inertia of labor in contracted pelvis is in a sense a protective phenomenon which should not be violated in this manner.   As for the induction of labor by this method, it is informative to note that the authors have met with little success.   We have not used it for this purpose except in the rare instances in which there is a long lag after induction of labor by artificial rupture of the membranes.—Ed.)

of the vertebral column, either very gross in the form of spina bifida already described, or the milder forms, disturbed the alignment of the tail.

The authors have examined in some detail the various conditions which were to be satisfied for the production of the maximum number of defects in the pups born to these rats. The group of 100 female rats used in their experiments was composed of 2 series; both series received an injection of trypan blue *during* pregnancy, but the second, in addition, had received a variable number of injections *before* conception. In the 1 series of rats receiving treatment *during* pregnancy only, 6 in a total of 186 pups (that is, 3 per cent) born to all mothers showed congenital malformations. These 6 defective rats were the offspring of mothers injected on the 8th or 9th days of pregnancy; in a total of 20 pups born to mothers treated on the 8th day of pregnancy, 4 were defective, while 2 abnormal pups in a total of 26 (that is, 7.6 per cent) were recorded in the litters of mothers treated on the 9th day of pregnancy.

In the 2nd series of rats, receiving an injection before conception as well as an additional injection during pregnancy, the incidence of abnormal pups was 25 per cent. When the mothers were injected on the 6th or 7th days before conception, as well as on the 8th or 9th days of pregnancy, respectively, then the incidence of malformations was greatly increased to 65 per cent in the former instance and 80 per cent in the latter. If rats received an injection on the day before conception only, the incidence of malformations was 25 per cent, and when treatment was given on the day of conception, then the incidence was 11 per cent. Rats injected only on the 16th day before conception gave birth to pups which developed jaundice within the first 3 days of life.

Having examined the several factors which may enhance or reduce the incidence of congenital malformations in trypan blue injected rats, it now remained for the authors to ascertain whether or not these experiments could in any way aid understanding further the epidemiology of maternal rubella as it concerns the pathogenesis of congenital malformations in human infants. In introducing this phase of their inquiry the authors present an extensive and valuable survey of available information on this subject. In the course of this review of the literature the authors recall that a few cases have been recorded where the mother contracted rubella before conception and still gave birth to a defective infant. The authors believe that these exceptional cases are not to be dismissed lightly as further analysis may reveal that therein may be found an important clue to the mode of action of rubella in the production of congenital malformations.

In applying the results of their studies on rats to the interpretation of the epidemiology of maternal rubella, the authors make the following tentative suggestions: first, in a random group of well nourished healthy women infected with rubella during the first 2 or 3 months of pregnancy, it can be expected that a considerable number will not give birth to defective infants; second, in such a group of women, a steep increase in the incidence of congenital defects suggests the existence of antecedent physiological operations; third, these antecedent physiological disturbances may be induced before pregnancy and persist for a variable period and sufficiently long to provoke defects in a small number of

malnutrition. The circulation of such particles, they believe, could lead to a variety of consequences, depending upon the state of reactivity of the organisms, upon the physical and chemical properties of the particles and upon the acuteness or chronicity of the process which permitted the particles to be poured into the circulation in greater or lesser concentrations over a shorter or longer period of time.

Acting on this hypothesis the authors endeavor to discover how far it is possible to produce some of the better known syndromes and the complications thereof by employing selected particles injected into animals in different physiological states.

The treatment of female rats with 1 cc. of a 1 per cent aqueous solution of trypan blue before conception and during pregnancy led to a high incidence of such congenital malformations as hydrocephalus, spina bifida, eye defects, and a lesser incidence of tail defects, meningocele, harelip and cleft palate, cranioschisis, ear defects, imperforate anus, club foot and dislocations of the fore- and hind-limbs. In a total of 697 fetuses, born in 118 litters, 19.2 per cent presented gross macroscopic malformations detectable at birth or soon thereafter, while 80.8 per cent appeared to be "normal." The distribution of defects in the litters was as follows: in 58 litters, comprising 352 pups, the young appeared to be normal in outward appearance. In the remaining 60 litters, comprising 345 pups, 134 were malformed.

Hydrocephalus. Fifty-one out of a total of 697 pups (that is, 7.3 per cent or 38 per cent in a total of 134 abnormal rats) were hydrocephalic. This represents more than a 4-fold increase over the number reported by Richardson and Hogen who produced hydrocephalus in rats by nutritional methods (J. Nutrition, 32: 359, 1946). In the present authors' series hydrocephalus occurred unassociated with any other defects in 28 pups, while in the remaining 23 it was combined with 1 or more other anomalies. In the majority of cases the hydrocephalus could be detected at birth. Serial sections of the brain revealed a completely communicating ventricular system. This suggested that the immediate cause for the persistence of the hydrocephalus was a disturbance in the relationship between secretion and absorption of the cerebrospinal fluid.

Eye Defects. In 30 animals (4.3 per cent of the total 697 and 22.3 per cent of abnormal rats) the absence of the eye balls on one side was easily detected at birth. With the exception of 1 animal, this anomaly was associated either with hydrocephalus, meningocele, ear defects, harelip, cleft palate or spina bifida. Histological examination revealed the structure of the pathological eye to be closely similar to that depicted by Warkany in rats bred on Vitamin A free diet.

Spina Bifida. This was one of the commonest malformations, afflicting 6.1 per cent of the total of 697 pups born and 32 per cent of 134 abnormals. In 23 of these cases the malformation was unassociated with any other defect and in 20, spina bifida was combined with 1 or more additional malformations.

Tail Defects. Thirty-five pups (5.0 per cent of total born and 26.1 per cent of total abnormals) showed tail defects; some young were born with no tails while others manifested various degrees of shortening of the tail. Frequently, defects

MALFORMATIONS IN THE GENITO-URINARY TRACT INDUCED BY MATERNAL VITAMIN A DEFICIENCY IN THE RAT

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·A great variety of malformations was found throughout the genito-urinary tract of fetal and newborn rats from mothers maintained prior to and during pregnancy on vitamin A-deficient diets.   Anomalies of paraplasia, that is those abnormalities resulting from aberrant embryonic processes, were exemplified by fused kidneys and an occasional instance of stenosis in ureters and homologous genital ducts.   Aplasias, or anomalies characterized by failure of a structure to develop, were represented by several instances of failure of male accessory glands to appear, particularly seminal vesicles and bulbourethral glands, and in the complete lack of vaginal development in most of the females.   Malformations of hypoplasia, those resulting from arrest or retardation of an embryonic process, whether progressive or regressive in character, accounted for a majority of all abnormalities observed.   Retarded progressive development was exemplified by: late partitioning of the cloaca, tardy appearance of Müllerian ducts, and slow differentiation of the urogenital sinus.   Examples of arrested progressive development were: positional abnormalities of the kidneys, ectopic ureteric openings, incomplete caudalward growth of Müllerian ducts, hypospadias, and failure of testicular descent.   Hypoplasia in the sense of retarded or arrested regressive processes was seen in: persistence of heterologous genital ducts and retention of the urethral plate.   All malformed newborns and fetuses older than 18 days gestational age exhibited keratinizing metaplasia in epithelial derived from the embryonic urogenital sinus.

(See editorial note appended to previous abstract and also Warkany's article and the following discussion which appeared in the last issue of the Survey, pp. 693-703.—Ed.)

RUBELLA IN PREGNANCY AS AN AETIOLOGICAL FACTOR IN STILLBIRTH

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This paper is based on a survey made by the author in 1946 of the etiology of about one third of the stillbirths recorded in South Australia in the 7 years

infants born to such mothers; finally, it is unlikely that the defects which become manifest in infants born to mothers infected with rubella in the last trimester of pregnancy can be attributed to the specific infection. Rather does it seem that such defects are the consequence of events enacted in the mother either before conception or in the early months of pregnancy, but that these events are not necessarily related causally to rubella.

The first of these suggestions takes into account the individual differences known to exist in a random group as exemplified by their experiments in rats and as observed generally in most types of biological experiments; the second might serve to reveal the underlying differences in the defect rate observed in Australia and in the United States. In this connection it should be remembered that the epidemic of German measles which swept Australia during the war years, when nutrition was of necessity lowered not only on account of short supply of food, but also because of the long working hours and mental strain and anxiety inevitable during periods of such great emergencies and stresses; the third suggestion covers the experiences in which an attack of rubella preceded conception by a variable period of time. In the case of their own experiments, the authors know that whatever effects may be produced by trypan blue, these are dependent on the physiological conditions prevailing in the mother. In the absence of positive information relating to the passage of the virus of rubella through the placenta, the authors consider it not inconceivable that the type of metabolic disorder associated with rubella mediates its effects in a manner similar to that induced by trypan blue and not by the passage of the virus into the fetal tissues.

Finally the authors note that, as far as is known, no other technique is capable of producing malformations within such a short period of time and with such great consistency as that shown in the case of the technique described in this study. The trypan blue technique is sufficiently reliable to permit an intimate study of the pathogenesis of hydrocephalus, spina bifida and congenital malformations of the eye and of other parts of the body.

(Although this article may seem to many readers of theoretical interest only, it may very well have important bearing on many practical problems, such as for instance, the causation of abortion. Are abortions and congenital malformations usually due to defective germ plasm or to defective maternal environment? The authors, on the basis of this extensive and scholarly study, make a good case for the latter explanation by showing that the injection into pregnant rats of trypan blue, which does not traverse the placenta but simply alters maternal well-being, causes a high incidence of fetal abnormalities. During the past decade the pendulum has swung decidedly from the viewpoint that almost all congenital malformations and most abortions are due to faulty germ plasm to the belief that a very large proportion of these accidents are the result of defective maternal environment. This is an encouraging trend since most of these maternal deficiencies are amenable to correction.—Ed.)

1 in 47 is appreciably higher than obtained in the population at large, or, let us say, in a comparable number of pregnant women who ultimately gave birth to healthy living infants. As the author points out in his original article, the sending out of these questionnaires was beset with many procedural difficulties and it is understandable that no control series was attempted. This is unfortunate because it would have been most informative to know also the incidence of rubella in 760 pregnancies which terminated in normal infants.

The findings are nevertheless suggestive, especially the observation that when rubella was reported it was usually stated to have occurred very early in pregnancy, that is, at a time when injury might have been done to beginning embryological processes. The paper, however, as the author avows, is published only in the hope of stimulating further work,— a reminder that all prenatal history forms might well include a question about rubella. If this were carried out, the whole problem presented by this disease in pregnancy might in the course of time be clarified.—Ed.)

REPORT OF A SURVEY OF CHILDREN BORN IN 1941 WITH REFERENCE TO CONGENITAL ABNORMALITIES ARISING FROM MATERNAL RUBELLA

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During the months of June to September, 1947, the Queensland School Health Service conducted a survey of children born in 1941, with a view to determining the extent of abnormalities resulting from maternal rubella during pregnancy. Questionnaires were delivered to 9674 mothers of children attending state primary schools, denominational primary schools, opportunity schools and grades, the School for the Blind and Deaf, private schools and institutions. Of these, 7822 were returned completed. It was learned that 21,509 children were born in Queensland in 1941. It is seen then that information was received concerning at least ⅓ of these children—enough to allow some idea to be formed of the extent of the epidemic and its resultant effects. Altogether there were 262 cases in which mothers were certain they had contracted rubella during that particular pregnancy. Of these, 134 were in the Brisbane area; the remainder of the children attended country schools throughout Queensland. Of those in Brisbane schools, 129 were examined clinically, the remainder being unavailable for examination. Of the 129 children examined, 51 had some abnormality. Of these, at least 37 could be classified as having a serious defect. These include all deaf mutes, mental deficients, congenital cardiac patients and children with cataracts. Eleven children had 2 or more serious abnormalities. Of the 128 cases from the country, there were 36 mothers who stated that their children had congenital abnormalities. It was impossible to examine these children owing to the great distances between the patients but if one can draw conclusions from the city group there is no great discrepancy between the mothers' statements and the

1939–45, with special attention to the incidence of infectious diseases during pregnancy. There were 2156 stillbirths registered from 1939 to 1945 and permission was given to send questionnaires to 1265 of the mothers, and 760 replies were received. One of the mothers had had stillborn triplets, and 2 had had stillborn twins, so the number of stillbirths resulting from the 760 pregnancies was 764. In the 760 pregnancies studied infectious diseases occurred as follows: influenza and its complications, 32 cases; pneumonia and upper respiratory infections, 5 cases; rubella, 16 cases including 2 who also had mumps and 1 who also had varicella; mumps, 2 cases; morbilli, 1 case; mumps and whooping cough, 1 case; varicella, 1 case; whooping cough, 1 case. The only infections with comparable incidences were rubella and influenza, and of course influenza is a relatively common disease. Bearing in mind the limitations of the data, none of the infectious diseases mentioned appeared to show any predominance in the early months of pregnancy such as is manifest with rubella.

The series is too small to be statistically significant, and in only 9 of the 16 cases was the diagnosis of rubella made by a doctor. Further, in 3 instances, there was a double infection during pregnancy, making it difficult to assess the respective roles of the diseases and the etiology to stillbirth. On the other hand, when the cases are arranged in order of the stage of pregnancy at which the mother contracted rubella, the striking fact emerges that in 13 of the 16 cases the infection occurred in the first 4 months of pregnancy—i.e., during the so-called "critical period" for the production of congenital abnormalities by rubella. Investigation of the 16 cases showed that in 8 there was no known cause for the stillbirth other than rubella.

When a woman contracts an infectious disease during pregnancy, from the viewpoint of the embryo a number of possibilities may be envisaged: (1) the embryo of fetus may be unaffected; (2) as a result of the direct action of the noxa or the indirect effect of the associated pyrexia, the embryo or fetus may die, and an abortion, miscarriage, or stillbirth may result according to the stage of gestation; (3) occurring early in pregnancy the infection may lead to congenital abnormalities, such as heart disease, as well as exerting a general deleterious effect on the embryo. The damaged embryo may then (a) be unable to survive to full term and, as mentioned above, abortion, miscarriage or stillbirth will ensue; (b) live to full term but be unable to survive the hazards of the birth process, so that a stillborn infant is born; or (c) live to full term and be born alive, resulting in a congenitally defective infant. So far as stillbirths, subsequent to maternal rubella are concerned, the evidence presented here and the case of Goar and Potts (Am. J. Ophthal., 29: 566, 1946) suggest that mechanism 3 (b) is the most important—the embryo being so affected by the rubella virus early in pregnancy that it dies at birth. This view will be confirmed if necropsies on stillbirths associated with proved maternal rubella reveal congenital malformations identical with those known to be caused by this disease.

(It will be noted that in these 760 pregnancies, all terminating in stillbirths, 16 women gave a history of rubella, or 1 in every 47. Now during the period covered by this investigation, an epidemic of rubella struck Australia and one wonders whether this incidence of

however, in the Massachusetts study, we consider only cases of rubella which occurred in the first trimester of pregnancy, a more significant figure is obtained because in 22 such cases, 5 infants had serious defects, or 22.7 per cent.

Only when we have more figures of this kind can we settle the perplexing problem of therapeutic abortion in these cases on an intelligent and factual basis.—Ed.)

MATERNAL MEASLES, MUMPS, AND CHICKENPOX AS A CAUSE OF CONGENITAL ANOMALIES

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Lancet, 1: 746–749, May 15, 1948

The development of congenital anomalies in babies born of mothers who have had virus diseases in pregnancy is worthy of intensive investigation. Many of the reported anomalies are extremely serious. Some of them, such as hydrocephalus and certain types of congenital heart disease, usually lead to serious disability and premature death. Most of the more significant anomalies impose severe financial handicaps on the parents. The community burden is often great because the afflicted children commonly need institutional care, special and costly educational facilities, frequent treatment in hospitals or otherwise at public expense, and in some cases, such as the blind and the deaf, financial aid. The extent and true significance of the psychic trauma suffered by those having anomalies, as well as by their parents and siblings, is incalculable.

The authors have made a preliminary investigation of measles, mumps, and chickenpox as causes of congenital anomalies. In Milwaukee these diseases are legally notifiable to the health department. Interviews by public health nurses were obtained with the 533 women who had had these diseases during the 4 years 1942–45. In this group there were 665 children born either before the onset of the disease or conceived and born after the disease was over. Among these children were 6 with congenital abnormalities, making the incidence .9 per cent, but dental abnormalities and slight mental retardation were not considered. There were 33 children who had been born of pregnancies in which the mother had had 1 of the 3 virus diseases. There was only 1 anomaly in this series and that was a unilateral harelip in a child whose mother had had measles in the 4th month of pregnancy. Since there were only 7 children born after maternal measles, the rate of congenital anomalies in this series following measles is 14 per cent or more than 15 times that in the normal group. The authors realize that this single anomaly might well be a chance occurrence but their measles series is obviously too small to warrant any statistical interpretation on the basis of probability.

The authors are fully aware that their series is too small for definite conclusions to be drawn. They have published their study in the hope that others will in-

clinical findings when the children are examined. Of the 36 children stated to have abnormalities, 19 were said to suffer from varying degrees of deafness. There were 8 cases of eye abnormality, 3 children were said to be mentally deficient and 2 were stated to have congenital heart disease.

In addition, of 40 children born in 1941 attending the school for the deaf and the blind, 26 gave a history of maternal rubella. Several of these had other abnormalities. The remaining 14 had no other abnormalities. Of these 14, in 11 cases the parents stated that their children were born deaf. Meningitis, hereditary factors and morbilli were given as causes in the remaining 3. As a control group, 1000 children attending state schools whose mothers were certain that they had not suffered from rubella during that pregnancy were examined. In these there were 18 children with abnormalities; 12 with eye defects, 2 with congenital heart disease, 3 with high frequency deafness and 1 with mild deafness.

Despite the lack of experimental evidence, there is sufficient clinical evidence in this and other reports to show the grave risk of exposure of the pregnant woman to rubella. The following measures and certain criticisms are presented: 1. Rubella might be added to the list of notifiable diseases. 2. Deliberate exposure of all girls to the disease might be practiced. This would depend on the availability of the disease, but otherwise seems feasible. 3. Inoculation with rubella might be developed. Suitable techniques are not yet available. 4. Exposed pregnant women might be treated with immune globulin. The efficacy of this measure has not yet been established. 5. Pregnancy might be terminated if rubella had been contracted in the first 4 months—a certain method, but its justification is debatable. 6. A warning might be given to all pregnant women, or women thought to be pregnant—the diagnosis in the danger months is not always definite—to avoid exposure. There is no bar to its implementation.

(In the editorial note appended to the preceding abstract, the question was raised as to the extent of the Australian epidemic of rubella, especially whether an incidence of 1 in 47 pregnancies, which obtained in a series of stillbirths, was higher or lower than was met in the population at large. From the figures reported in this paper by Patrick, namely, 262 cases in 7822 pregnancies, or 1 in 30, it may be seen that the frequency of the disease in Swan's series of pregnancies ending in stillbirths was actually lower than was encountered in Patrick's 7822 mothers,—presumably a representative sample of the population at large. In so far as my arithmetic can go, this would seem to be evidence against Swan's contention that rubella early in pregnancy may be a cause of stillbirth at or near term.

Patrick's study is a valuable one because, instead of starting with a series of congenital malformations and ascertaining how many mothers of these babies had rubella during gestation, he starts with 262 cases of rubella in pregnancy and inquired how many infants were seriously defective. This is the figure we would all like to know. Of the 129 infants examined in the Brisbane area, 37 had a serious defect or, 28.7 per cent, while in the country group the number of infants reported as having abnormalities was 36 in 128 cases, or 28.2 per cent, an exact check.

A similar study had been reported in this country by Oher, Horton and Feemster (Am. J. Pub. Health *37*: 1328, 1927). Since rubella occurred in Massachusetts during 1941 in twice its usual frequency, questionnaires were sent out to all women of childbearing age who had been reported as having rubella that year as well as to some 6000 physicians. Forty-nine women were reported as having had rubella in pregnancy. Six of the babies from these gestations presented congenital malformations of serious degree, that is, 12.3 per cent. If,

Rh-positive, (tested with anti-D only) who succumbed of clinically and pathologically typical erythroblastosis fetalis. Postpartum the mother's serum showed agglutinating antibodies against Rh-positive cells. Her third pregnancy resulted in a full term male infant, Group O, Rh-positive, CDe/cde, who survived without treatment and showed no clinical evidence of erythroblastosis. Postpartum the mother's serum showed blocking antibodies only in a titer of 1:32 against both CDe and cDE cells.

Case 2. Mrs. L., Group O, Rh-positive, CDe/CDE; Mr. L., Group A, Rh-positive, cDE/cde. Her first pregnancy in 1940 resulted in a full term male infant, Group O, Rh positive, CDe/cDE, who was normal. Following delivery she received 2 transfusions: 1 Group O, Rh-positive CDe/cDE, and the other Group O, Rh-positive, cDE. Her second pregnancy resulted in another full term male, Group A, Rh-positive, CDe/cDE, who was normal. Her third pregnancy resulted in a full term male, Group O, Rh-positive, CDe/cDE, who had clinical evidence of erythroblastosis and who survived after 6 transfusions of Rh-negative blood. The mother's serum contained agglutinating and blocking anti-E antibodies, and anti-c blocking antibodies. In 1947 a fourth full term male was born who was Group O, Rh-positive, CDe/cde and had weak antibodies against Rh-positive CDe/cDE cells and Rh-negative cells. The child, however, was clinically normal and had survived. The mother's serum exhibited blocking antibodies in low dilutions (1:4 to 1:16) against CDe/cde, CDe/CDe, and cde/cde cells.

For Case 1 any explanation must be purely conjectural in the light of our present knowledge. In Case 2, however, there is a possible explanation. The mother was isoimmunized against the relatively rare and therefore presumably weak antigens, E and c. However, only anti-c was effective against the fetal erythrocytes and apparently this antibody was not present in sufficient quantity to appreciably damage the fetal erythrocytes.

(Most of us, I imagine, have had one or more experiences with cases such as the above, that is, cases in which the outcome for the baby was at variance with the antibody titer of the mother. The practical lesson to be drawn from these cases, as I see it, is that we must be extremely wary about basing prognosis solely on antibody findings.—Ed.)

THE PRODUCTION AND PROPER USE OF Rh TYPING REAGENTS

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In the past 5 years Rh typing has been recognized as an important and a practical laboratory test. The blood grouping laboratory of Boston has grown at a phenomenal rate since its formation in 1942. Similar laboratories, in hospitals,

vestigate the occurrence of anomalies in the normal population, as well as in the children of mothers who have had virus diseases in pregnancy. Epidemiologists could visit married women notified as having virus diseases to verify the diagnosis and ascertain whether there is coexistent pregnancy. Birth and stillbirth certificates could then be checked against the file of such cases, with the epidemiologist visiting and examining living children as soon as possible after birth and at yearly intervals for at least the next 4 years. Through such an approach it would be possible to accumulate sufficient data to determine the true numerical probability of the development of anomalies in relation to type of disease, character of anomaly, and period of gestation. The number of pregnant women with so-called "childhood contagious diseases" will be proportionately higher in small towns and rural areas than in the large urban centers. Consequently the problem of anomalies should be investigated in rural as well as urban areas, if the data required for sound statistical interpretation are to be accumulated as rapidly as possible.

MATERNAL ISOIMMUNIZATION WITHOUT EVIDENCE OF CLINICAL ERYTHROBLASTOSIS FETALIS IN THE NEWBORN

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One of the many unsolved problems in the field of Rh-Hr isoimmunization is why an occasional infant possessing antigenic factors against which the mother is isoimmunized is born healthy and never subsequently exhibits evidence of erythroblastosis. If an explanation could be found for this phenomenon it might be possible to develop more effective methods of treating sensitized mothers in an effort to minimize deleterious effects on the fetus.

There are a number of cases reported in the literature of normal Rh-positive infants born to Rh-negative mothers with blood containing Rh-antibodies. There are, however, according to the authors, no cases in which there is unequivocal proof that the mother had borne previous erythroblastotic infants. Nor are there any cases in which there is proof that the normal Rh-positive infant possessed antigenic factors against which the mother was isoimmunized. The authors present 2 such cases, for one of which a tentative explanation is offered.

Case 1. Mrs. M. N., Group O, Rh-negative, cde/cde; Mr. G. N., Group O, Rh-positive, CDe/CDe (negative to anti-c). Her first pregnancy in 1942 resulted in a full term male infant, Group O, Rh-positive, CDe/cde, who had jaundice which disappeared without therapy. The child has been perfectly well since. Her second pregnancy in 1945 resulted in a full term female, Group O,

practice in many hospitals and blood banks to use an 87 per cent serum which is much more common and more easily obtainable, and contains both the Rh′ (anti-C) and the Rh₀ (anti-D) factors. The author points out on the other hand that in a large group of cases there is a large number of individuals who will be identified by 87 per cent serum as being Rh-positive, when actually they may be negative to Rh₀ (D) which is the most common and most important Rh factor for sensitization. He recommends, therefore, that it would be much wiser to use only an 85 per cent anti-D serum in all obstetrical clinics and possibly in all blood banks.

For the production of Rh typing reagents there are 3 sources of human serum available. First, the accidentally immunized man or woman who has a high-titered serum (in the case of the latter pregnancy being the most common cause for such sensitization); second, the woman who has been sensitized but has low titered antibodies but can be restimulated to the production of more potent agglutinins; and third, volunteers, of proper blood type (chiefly Rh-negative, although Rh′ and Rh″ subjects can also be used) who may be stimulated through injection of Rh-positive blood. Obviously the patients who have high-titered serum in pregnancy are most useful at the end of gestation or shortly thereafter. The presence of debility or anemia following childbirth, unfortunately makes it difficult to obtain much of this type of blood, and there is a rather rapid fall in anti-Rh titer which tends to occur in most women within a few months after the end of gestation so that their blood does not remain valuable for too long a time. The author therefore recommends that it is desirable to have a large panel of donors, either women restimulated by suitable injections of Rh-positive blood, or male subjects initially stimulated and later restimulated, so that the useful Rh reagent may be obtained frequently and in sufficient volume. An initial stimulation can be produced by as little as 50 ml. of whole blood given intravenously. Intramuscular or subcutaneous blood has not proved satisfactory. The author points out that the use of a cell-free Rh antigen would be ideal but no uniformly satisfactory free source has been discovered to date by the many workers in this field, and therefore fresh Rh-positive cells remain the only satisfactory stimulus. They may be given in very minute amounts to properly sensitized individuals, that is, as little as 0.1 to 0.2 ml. of blood. Larger amounts may be satisfactory but the author has observed disturbing chills, headache, pain in the back and even fever in highly sensitized individuals from as little as 1 ml. of whole blood injected intravenously. The production of the rarer typing sera has not been satisfactory to date, so that for a source of these we are still dependent upon the identification of women sensitized by pregnancy with the specific incompatible factor.

The importance of the preservation of sterility in preserving Rh typing reagents is pointed out, together with the fact that the usual bacteriostatic or antibacterial agents caused relatively rapid deterioration of the Rh typing reagent. For saline agglutinins refrigeration is necessary but the hyperimmune forms which are heat-stable can often be stored at room temperature for long periods without much loss of potency. Dilution will also cause a loss of potency but it is possible to mix these reagents with albumin in a proportion of roughly about 1 to 1 which not

under the sponsorship of the city, county, or state medical groups, have been organized all over the country. In fact, it has become an accepted public health responsibility in many states to type all women prenatally, in an effort to protect the Rh-negative individuals from sensitization to the Rh factor, should blood transfusion be necessary during pregnancy or in the puerperium. Since large numbers of men, women and children at some time or other have a serologic test performed in state laboratories, the author feels it would be a simple and protective measure to carry out blood grouping and Rh typing on all such specimens. Through this the individual, knowing his or her own blood type and Rh blood type, could help the physician to avoid improper transfusion or blood injection which in so many instances has led to serious transfusion accidents and in pregnancy cases, to serious harm to infants of sensitized mothers. The Rh-negative women being so identified, could be watched more carefully by their obstetricians; and with suitable testing of the husband and of the patient's blood, particularly in the second or later pregnancy, early detection of Rh antibodies may help avoid some of the catastrophes occurring at term to infants with erythroblastosis fetalis. For all these purposes the proper use and the increased production of Rh typing reagents are a necessity. Further work is necessary in order to offer the fullest protection to everyone.

The proper use of anti-Rh sera requires that the tests be performed on relatively fresh cells, that certain precautions and technic be observed, that sera for test-tube testing on saline suspended red cells be recognized as different from sera containing the hyperimmune component acting only on cells suspended in plasma, serum, or other protein media, such as albumin. In the author's hands the slide test has proved one of the most satisfactory and most rapid methods of Rh typing. It involves the use either of oxalated whole blood or of blood taken directly from a finger prick and is done relatively easily and most rapidly if the serum is sufficiently potent and avid to give macroscopic agglutination of Rh-positive blood within 2 to 3 minutes. The slide testing serum has the advantage that it is more abundant and more stable than other testing sera. To avoid error, it is advisable that controls be set up, such as known Rh-positive and Rh-negative cells which can be tested in the laboratory at regular intervals, and that a potent serum be used with a 40–50 per cent suspension of cells. Another important consideration in the proper use of Rh typing reagents is the knowledge that individuals having the rare subtypes Rh' or Rh" (C and E) are just as likely to develop sensitization to the common Rh blood type, Rh_0 (D) as are Rh-negative persons. For transfusion purposes, therefore, it is important to test the recipients of blood and women undergoing prenatal tests with an anti-Rh_0 (anti-D) or so-called "standard" Rh typing reagent. Anyone negative to this reagent is susceptible of sensitization to this common factor which is present in 85 per cent of the white population.

Although it is difficult to sensitize an RH_0 individual who lacks the Rh' (C) or Rh" (D) factors, to these rare types (and statistically, the chances of doing so are very small), such a difficulty may occasionally become important in the women with obstetrical complications. For this reason it has become common

ISO-AGGLUTININS IN CORD BLOOD

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Investigations on the relationship of Rh antibodies in the maternal and infantile blood have once again drawn our attention to the question of the relationship of anti-A and anti-B iso-agglutinins in the maternal and infantile circulation. The fact that the fetus develops its blood group antigens very early, and after having provided her share of necessary genes, according to the Mendelian law, the maternal host has no further influence on them, has been well established. The origin and development of the iso-agglutinins in late prenatal and early postnatal life are not· so clearly defined. Further observations on this subject, based on the investigation of 355 samples of cord blood and corresponding maternal blood, are recorded in this paper.

When the mother is of group O, the alpha and beta agglutinins appear more frequently in the cord serum than they do when the maternal group is A or B. The complete agglutinogen-agglutinin A B O blood group pattern is found in only 38.8 per cent of cord blood samples, the agglutinins being absent from or incompletely developed in the remainder. Agglutinins incompatible with the child's red cells were found in 4 samples of cord blood. These were possibly immune antibodies produced in the maternal serum by group-specific substances from a secretor fetus, which by virtue of relatively small molecular size were able to traverse the placenta. An agglutinin which was incompatible with the mother's red cells was found in 1 sample of cord blood. Analysis of the figures obtained suggests that the evidence favoring maternal origin of agglutinins in the cases in which they could, in relation to the blood groups of mother and child, be of either maternal or infantile origin.

BLOOD GROUPING AND Rh TYPING IN A STATE PUBLIC HEALTH LABORATORY

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The Massachusetts Department of Public Health is engaged in a large scale blood grouping and Rh typing program. This program arose in response to the

only helps conserve the rather expensive fraction of blood, but tends to improve the avidity and titer of the reagent. For this purpose bovine albumin has been found most satisfactory and cheapest.

Finally, it is important to neutralize the natural anti-A and/or anti-B isoagglutinins if the donor belongs to Group O, A, or B. The author does this chiefly with Witebsky's AB substances. However, the neutralization by this method does not seem to be always a stable process so that other methods must be sought for, such as the proper preparation of saliva from secretor individuals of the proper group, or the use of the blood cells themselves. These two last procedures, however, are rather difficult and troublesome; so that the use of Witebsky's substance is generally preferred.

(As most of our readers are fully aware, this paper comes not only from an eminent authority on Rh problems but from a laboratory with a vast background of experience. The article therefore should be of great practical value to anyone who is concerned in any way with the technic of Rh typing.

One of the problems which almost any blood bank faces is the difficulty of maintaining at all times an adequate supply of Rh negative blood. This is especially true of smaller hospitals, but in any hospital the supply may just happen to be low at a time when an Rh-negative patient with a massive hemorrhage demands perhaps 2 or 3 liters of blood. We have met this situation in Baltimore very satisfactorily, we believe, by establishing an Rh-negative blood bank for the entire city,—in addition, of course, to blood banks maintained individually by the larger hospitals. This is an outgrowth of the Baltimore Rh Typing Laboratory where in the course of its existence over 40,000 pregnant women have been typed. Hence, the names and addresses of a huge number of Rh-negative, Group O, women are on file, and these have been successfully solicited as donors for the bank. If a hospital without a blood bank requires Rh-negative blood in a hurry, or if any hospital has exhausted its supply and is faced by an emergency need, the Baltimore Rh Typing Laboratory is telephoned. Forthwith things move fast. A person to whom this responsibility has been delegated is notified, secures the blood from the refrigerator and takes it to the curb in front of the Laboratory. Meanwhile, the telephone operator notifies the Baltimore police, who have kindly agreed to collaborate, and the nearest radio police car is dispatched to the Laboratory, picks up the blood at the curb and speeds to the hospital which puts in the call. The blood has been so treated that it is ready for immediate use. Twenty-four hour service, of course, is available.

From the initial telephone call, the blood can be delivered to any hospital in Baltimore within 25 minutes, to most within 15 minutes. Recently a record was set as follows. A telephone call for blood came from an obstetrician in a Havre de Grace hospital, 35 miles north of Baltimore. Haste was urged. With the collaboration of the Maryland State police as well as the Baltimore City police, the blood was delivered to the door of the Havre de Grace hospital exactly 35 minutes after the call was received.

With hemorrhage assuming No. 1 place as a cause of death in childbearing, services such as this promise much in the immediate saving of lives. They also promise much in a prophylactic way in long term perspective, that is, fewer women will be sensitized to the Rh factor as the result of emergency transfusions.

The Baltimore Rh-Negative Blood Bank was started only on July 12, 1948 and hence it would be premature to speak conclusively about its success. Thus far, however, it has functioned most satisfactorily and we see no difficulties ahead. Finally, a word about the person who is entitled to chief credit for this undertaking. Both the Baltimore Rh Typing Laboratory and the Rh-Negative Blood Bank have been worked out almost singlehanded by Dr. Milton S. Sacks, the well-known hematologist of the University of Maryland School of Medicine and all we obstetricians in Baltimore consider them a splendid tribute to his insight and efficiency.—Ed.)

able to test not only for positivity and negativity but also to subtype all Rh-negative women, their husbands and children. Any woman who gives a history of abortions or other accidents of pregnancy, even though she tests positive with the 85 per cent serum, is subtyped.

Of 2507 Rh-negative women tested in this laboratory, 46 have borne erythroblastotic infants, the infant mortality with either class being about 50 per cent. Seventeen have had stillborn infants. Nineteen normal infants were born to women having agglutinins and blocking bodies. There were 6 Rh-positive women who had erythroblastotic infants. Two of these children lived and 4 died. It was not possible to explain these anomalies although they might be due to differences in the blood groups. In 1 case it was not. A family was noted, 3 of whose members possessed the rare Rh' Rh" factor.

The author is disturbed that many hospitals still do not Rh type patients who are to receive transfusions, and that transfusion reactions are still being reported. In Passaic County an Rh-negative blood donors' club has been set up which now has on its rolls more than 80 active members. All names of Rh-negative persons are sent to the Secretary of the Passaic County Medical Society who in turn contacts these persons, suggesting membership in the club.

THE SIGNIFICANCE OF THE PAUCITY OF SICKLE CELLS IN NEWBORN NEGRO INFANTS

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A study was made of sickling in 452 consecutive negro newborns and their mothers; 8 per cent of the mothers and 8.4 per cent of the infants showed sicklemia. The red cells of mothers with sicklemia showed 84 to 100 per cent sickling, while those of the newborns showed only 0.5 to 29.5 per cent. The red cells of the latter also required a longer time to attain maximum sickling. The greater affinity of fetal hemoglobin for oxygen should not account for the low percentage of sickled red cells in newborns with sicklemia, since the maximum percentage of sickling could not be raised over that of the sealed preparation by use of the gas chamber method where oxygen can be excluded entirely from the system. It might be thought that immaturity of many cells in the newborn would reduce the sickling tendency, as there are in the literature reports that normoblasts and even reticulocytes fail to sickle. Careful study by the author (1947, In press) has shown that, while the velocity of sickling may be retarded in immature cells, the percentage is the same as in older ones. The blood of these infants contained no high percentage of immature cells and another explanation must be sought. It

needs of the State blood bank, which now collects some thousand bloods each week. This is done by means of two mobile blood bank units collecting blood 5 days each week from the various communities throughout the state. All donors are typed in the field by the slide method and a pilot tube of clotted blood is rechecked independently at the Diagnostic Laboratory by the tube method. The chance of discrepancy from time to time, especially in Rh typing, is eloquent evidence of the value of this double checking in any blood grouping and Rh typing program, and enlightening information has been gained by complete investigations of all disagreements.

In the first 10 months of its existence the Rh typing department of the Diagnostic Laboratory typed 19,442 bloods of which 83.1 were Rh-positive, 16.1 per cent Rh-negative and 0.8 per cent rare Rh+. This latter group consisted of bloods which are negative with 85 per cent (anti-Rh_0 or anti-D serum), but positive with 87 per cent (anti-Rh_0' or anti-C+D serum).

The field laboratory and the Diagnostic Laboratory disagreed on 50 blood groupings of the ordinary blood groups. All these discrepancies were eliminated by rechecking. On the other hand, the 2 laboratories disagreed on 140 Rh typings of which 23 could not be explained.

In addition, the Department evaluates laboratories in the state desiring approval for blood grouping, Rh typing and crossmatching. The results of this evaluation reveal an uncomfortably high percentage of errors, particularly in Rh testing. This indicates the great need for more adequate supervision of laboratories performing blood typing tests.

Finally, the program includes also blood grouping and Rh typing of prenatal bloods as requested by physicians. This test is conveniently performed upon the same specimen submitted for the required prenatal test for syphilis. This service is valuable as a state public health activity and the volume of the work is growing. It is hoped that disastrous results which have previously occurred when Rh-positive blood has been given to pregnant Rh-negative women will be prevented by this program, as well as more intelligent management of mother and child made possible.

IS THE Rh FACTOR A PUBLIC HEALTH LABORATORY FUNCTION?

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The author and physicians of Passaic County, New Jersey, are thoroughly convinced that the Rh factor is indeed a function of this particular public health laboratory. Their experience has shown that a central laboratory is highly desirable for routine Rh testing of antepartum women. They have found it advis-

PENICILLIN IN DROPS FOR PROPHYLAXIS AGAINST OPHTHALMIA NEONATORUM

A Single Instillation Method

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In a previous communication the author reported that penicillin in drops had been found to be effective in the prophylaxis of ophthalmia neonatorum when a method of multiple instillation was used. That method required 4 instillations: 1 immediately after birth and 1 daily for each of the first 3 days of life. Mechanical cleansing of the eyes was carried out before the first instillation. The present study was undertaken to evaluate the use of only 1 instillation of penicillin with, as before, mechanical cleansing of the eyes.

For a 5-month period (beginning February 1, 1947) penicillin in drops was used for prophylaxis in the eyes of each newborn infant delivered at the John Gaston Hospital, Memphis, Tennessee. Penicillin was used in the form of the crystalline sodium salt of penicillin. A concentration of 2500 units per cc. of sterile isotonic sodium chloride was used. Sterile isotonic sodium chloride solution was used for irrigation of the eyes. Prophylaxis of the eyes of each newborn infant was carried out in the delivery room within 1 hour after birth. The eyelids and adjacent area of the newborn infant were cleansed of contaminating secretions by gently wiping with a large ball of sterile cotton from the inner canthus outward. The eyes were closed at the time. Gauze was then used on the fingers for traction to hold the eyelids while each eye was flushed thoroughly with sterile isotonic solution of sodium chloride. Four drops of penicillin solution were then instilled into the conjunctival sac of each eye. When an infant exhibited pus in its eyes during the neonatal period, a culture was taken from the conjunctival sac of each eye.

A total of 1177 infants was studied in the nursery. All neonatal deaths occurring among the infants born during the period of investigation were excluded. Thirteen (1.1 per cent) of the 1177 infants exhibited pus in 1 or both eyes after penicillin prophylaxis. All degrees of pus, no matter how slight, were included. The day of life upon which pus was first observed varied from the 3rd to the 12th day, the average being 7.2. The incidence of 1.1 per cent of infants exhibiting pus in the eyes while in the nursery is low as compared to the incidence after silver nitrate prophylaxis (6.0 per cent). All cultures of the 13 infants who exhibited pus in the nursery were positive. Two-thirds of the organisms isolated were staphylococci.

Abnormalities other than the presence of pus were evaluated. Two hundred infants were followed to note the incidence of eyelid swelling, conjunctival red-

is well established that human fetal hemoglobin differs chemically from adult hemoglobin. Differences have been demonstrated with respect to alkali denaturation (Monatschr. f. Kinderh., **31:** 228, 1926), histadine content (J. Biol. Chem., **156:** 283, 1944), immunological properties (Arch. Path., **30:** 873, 1940), the oxygen dissociation curve (J. Clin. Invest., **20:** 739, 1941), crystallization (Arch. fisiol., **29:** 289, 1931), and sedimentation constants and electrophoretic mobilities (J. Biol. Chem., **153:** 301, 1944). Brinkman et al (J. Physiol., **80:** 377, 1934) have shown that newborn blood contains about 80 per cent of the fetal alkali resistant hemoglobin. Trought (Arch. Dis. Childhood, **7:** 259, 1932) in a similar investigation found that it disappeared as early as $4\frac{1}{2}$ months. The theory that at once presents itself is that fetal hemoglobin is unable to produce sickling, and that the sickling trait progressively becomes 100 per cent with the gradual formation of the new red cells containing the adult type of hemoglobin which possesses the sickling property. This hypothesis is further strengthened by the fact that the estimated life span of the erythrocyte is 4 months (Wintrobe, M. M.: Clinical Hematology, 2nd ed., Phila., Lea & Febiger, p. 105, 1946). Whether this last instance represents the usual course of events can be decided only by following the percentage of sickle cells from birth through 1 year in a series of infants. Eleven infants with sicklemia have been followed for 4 months at monthly intervals since birth. Sickling increased progressively to reach an average of 90 per cent at the age of 4 months. Further evidence to support the above theory can be obtained if one considers that since an oxygen tension of 45 mm. of mercury is taken to be the threshold for sickling in patients with sickle cell disease (Bull. Johns Hopkins Hosp., **67:** 309, 1940), the much lower oxygen tension that occurs in utero should cause complete sickling and thus be incompatible with life. In fact, if the same low tension of 16 mm. is achieved in the human fetus as in the sheep, sickling in utero should occur even in those with the sickling trait only, since the oxygen tension threshold in these cases is estimated to be 18 mm. However, the authors could find no cases in the literature of pathologic findings of sickle cell anemia in autopsies of newborns and stillbirths. It seems likely then that fetal hemoglobin lacks the sickling properties of adult hemoglobin, thereby preventing automatic extinction of sickle cell disease from deaths in utero, and partially protecting the infant in the first 4 months of life during which time it gradually disappears from the blood.

OPERATIVE OBSTETRICS

THE ELECTIVE USE OF KIELLAND FORCEPS IN MANAGEMENT OF OCCIPITOPOSTERIOR AND OCCIPITOTRANSVERSE POSITIONS

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Whatever method has been used in management of labor in occipitoposterior and transverse positions of the fetal head, the prevalent approach has been conservative, with general agreement that before any attempt to terminate labor full dilatation of the cervix with strong labor pains should have occurred for 2 hours or more, or that there should be obvious signs of maternal or fetal distress or both.

The present study analyzes 2601 consecutive deliveries of private patients in which Kielland forceps were used in 547 instances of occipitoposterior and transverse positions. In most of the 547, the forceps were used as an elective procedure to rotate and deliver the fetal head as soon as, or shortly after, full dilatation was obtained.

With 2 exceptions, the forceps should always be applied in the original Kielland manner. The anterior blade is introduced well into the uterine cavity and then rotated into apposition with the fetal head, the tip of the blade thus describing a clockwise arc when the occiput is directed to the right side of the mother's pelvis and counterclockwise in the left position. In actual use, 2 fingers of the left hand are inserted into the vagina and between the cervix and the fetal head. The head should not be disengaged or disturbed in any manner. The tip of the anterior blade, pointing upward, is then inserted between the fingers in the vagina and the cervix. Frequently as the blade passes into the uterine cavity it encounters a resistance which examining fingers will find due to a constriction of the uterine muscle at the junction of the cervix with the uterine musculature. If delivery is too long delayed, this "temporary or functional contraction ring" may become the pathologic contraction ring. When this resistance is encountered the handle of the forceps is elevated and the tip of the blade passes readily into the uterine cavity, where it can be rotated and applied to the fetal head. The posterior blade is then inserted and articulated with the anterior blade.

The 1st exception occurs when a true contraction ring is present; it is then dangerous to attempt insertion of the blades by the rotation method, and the "wandering" method is advisable. Second, when the head is low in the pelvis and the occiput is directly posterior the blades are applied to the sides of the fetal head exactly as with classical forceps, keeping the markers on the handles directed toward the occiput. The head may then be rotated without difficulty and delivered with a single application of the forceps.

ness, and watery discharge. The degree of abnormality, slight, moderate or severe, was graded. During these days swelling of the eyelids was noted in 20 per cent of the infants; conjunctival redness in 37 per cent; and watery discharge in 0.5 per cent. Moderate and severe degrees only of these abnormalities were noted in this analysis.

At the time of the public health nurses' examinations at the patients' homes, between the 14th and 17th day, pus was found in the eyes of 2.9 per cent of the infants. Other abnormalities, conjunctival redness, swelling of the eyelids or a watery discharge, were noted in 1.5 per cent by the public health nurses.

There was no known instance of conjunctivitis caused by the gonococcus, either in the nursery or at home, in this series or the previously reported series using 4 instillations. The combined series constitute a total of 2138 infants studied after treatment with penicillin prophylaxis.

(Franklin is entitled to great credit for his pioneer studies on penicillin drops for the prophylaxis of ophthalmia neonatorum. Our own experience with this problem is now of 2 years' duration and covers in our own and another hospital over 6000 infants who have been treated prophylactically with penicillin in one form or another. It is my tentative feeling that Franklin is probably correct in maintaining that topical treatment, rather than intramuscular, is the most satisfactory, but we prefer penicillin ointment to the aqueous drops which he uses,—chiefly on the grounds that the ointment stays in the conjunctival sacs longer. Moreover, I believe our figures will show a much lower incidence of eyelid edema and redness than he has encountered with aqueous drops. Our experience with penicillin ointment, however, must be considerably augmented before any sweeping recommendations can be made.—Ed.)

(1.46 per cent), 3 were found due to anatomical conditions incompatible with life. Excluding these 3, the corrected neonatal mortality is 0.90 per cent. These 5 were ascribed to intracranial hemorrhage, and all occurred in cases that would usually be considered as "indicated" Kielland forceps deliveries. In the fetuses delivered by the "elective" use of Kielland forceps, such complications as marked molding of the fetal head, caput succedaneum, and cephalhematoma were almost entirely absent.

In only 6 instances delivery could not be effected by Kielland forceps; rotation was accomplished but traction did not result in descent of the head. Cesarean section was performed twice satisfactorily, and version 4 times with good results in 3. The 4th, not considered safe for section, resulted in fetal injury which developed into hydrocephalus of traumatic origin and death at age 2 years.

In occipitoposterior positions, the 1st stage of labor is prolonged and the character of the pains is more severe. As the writer has shown, and as Kushner and Wahrsinger have stated, the application of Kielland forceps early in the 2nd stage is safe for the mother, results in shortening her labor and in relief of pain, and is therefore a worthwhile procedure. For the fetus, early application is vital. Reports in the literature indicate 21 fetal and neonatal losses out of 134 instances, and 14 out of 200, in late application of Kielland forceps. In the present study there were 13 fetal and neonatal deaths in 547 cases, and it was felt that had delivery been effected earlier in all instances, the fetal loss would have approached zero. 4 tables.

(This is an instructive article from several points of view. In the first place, it will be noted that all Miles' 2588 consecutive labors in private practice were conducted by vaginal examinations. Yet the morbidity was low despite the inclusion in the series of a number of referred cases after attempts at delivery at home; and there was no death from outright puerperal infection although 1 patient succumbed as the result of pulmonary embolism. There can be no doubt that the danger of vaginal examination has been over-emphasized; it has been stressed, indeed, to such a point that it is difficult to persuade house staff members to perform vaginal examinations at all. Perhaps as a teaching policy this is a good thing, but on the debit side of rectal examinations can be charged many obstetrical mistakes stemming from lack of awareness of the true state of affairs. In any case in which the findings on rectal touch are not clear-cut and in every case of protracted labor, sterile vaginal examinations are indicated in as great a number as may be necessary to provide at all times full and accurate information. Because, in 9 cases out of 10, rectal examinations do provide this information, because they are more convenient and because they are less conducive to infection, they have rightly become the routine procedure in most obstetricians' management of labor, but as Miles has shown, vaginal examinations, under sterile conditions, are not as harmful as we used to think.

The second informative statement in the paper is that Miles recommends, on the basis of this large experience, the original Kielland method of application, that is, the insertion of the anterior blade with the tip upward, followed by a 180° rotation of the blade. Most obstetricians have hesitated to do this, fearing rupture of the uterus, and recommend the "wandering" or "gliding" method of application, that is, the same that is used with other types of forceps. The fact that Miles has employed the original method in such a large series of cases without mishap gives many of us courage to use this technique when indicated,—that is, in the transverse arrest of the head which time will not correct. With the reservations mentioned by Miles, it is certainly easier to carry out than the "wandering" or "gliding" method.

Rotation of the head may be accomplished by (a) rotation with traction—if the head is lying in the plane of greatest pelvic diameter, gentle rotation of the handles in a straight line and not with a sweeping movement will usually suffice to bring the occiput to an anterior position; (b) rotation with traction, which will produce rotation accompanied by descent of the head, where simple rotation does not readily work; (c) disengagement of the head with rotation above the pelvic brim. While this last would appear a radical procedure, the cephalic curve of Kielland forceps fits the fetal head so accurately that thrusting the head up and out of the pelvis does not disengage the head from the forceps. The head is readily rotated to an obliquely anterior position; traction with the resulting descent and further rotation brings the head to the desired anterior position, and delivery is effected.

There must of course be no cephalopelvic disproportion. Traction for delivery should be applied in the direction naturally taken by the handles of the forceps. Too great elevation of the handles causes deflexion of the head, necessitating too much force and possibly resulting in severe lacerations.

In these 2588 cases (2601 infants), all labors were conducted by vaginal examinations preceded by a vaginal instillation of 15 cc. of a 5 per cent aqueous solution of Mercurochrome. Among the 2499 vertex positions there were 594 occipitoposterior presentations. (24 per cent, compared with reports in the literature of 26–48 per cent). The 547 in whom Kielland forceps were used comprise 2 groups: 36 patients who were referred after attempts at delivery, including forceps, version and full doses of pituitrin, had failed, in all of whom the mothers were near exhaustion and the fetuses in evident distress or already dead; and 511 cases who were under the author's care all through pregnancy. In the latter, without waiting for a time limit or for signs of distress, when the cervix was fully dilated and the head deeply engaged in the pelvis, the patient was taken to the delivery room and prepared for delivery; under anesthesia the Kielland forceps were applied in the original manner and the head rotated and delivery effected.

There were no deaths from infection in the entire series. Total morbidity was 3.67 per cent. Among the 19 (3.47 per cent) instances of morbidity in those delivered by Kielland forceps, 7 were in patients brought to the hospital after long labor and attempts at delivery at home, with intrapartum infection before admission. Sulfa drugs (50 cases) and penicillin (6 cases) were used on indication only. Total mortality in the 2588 mothers was 6. In the 547 delivered by Kielland forceps there were 2 deaths, 1 of an eclamptic woman brought in comatose and moribund, and the other due to a pulmonary embolus.

Postpartum hemorrhage occurred in 1.09 per cent of the women delivered by the Kielland method and 1.07 per cent of the others. The only complication occurring more frequently among those delivered with Kielland forceps was laceration involving the rectum—5 cases, compared with 2 among those delivered by other means. All were immediately repaired and healed without complication.

Among the 547 babies delivered by Kielland forceps there was none under 1500 gm. Of the 5 stillborn, 4 were badly macerated. Of the 8 neonatal deaths

more extensions can be expected. The weight of the baby in this series was no factor in the incidence of rectal lacerations. Actually, the size of the baby was slightly smaller than the average clinic rate. Although the authors are unable to demonstrate it in their series they lean to the belief that a diminution in the size of the transverse diameter of the ischial tuberosities is probably an important factor in conducing the 3rd degree lacerations.

The authors' method of repairing 3rd degree lacerations is as follows: The repair is started at the apex of the rectal laceration, using interrupted sutures of no larger than 0 chromic catgut placed about 0.5 to 1.0 cm. apart. The knots are tied in the lumen of the bowel. This decreases the amount of catgut that is buried. *The sutures go through the entire rectal wall since it is so thin that it is* difficult to include only part of the wall and still obtain good approximation without tension. The interrupted sutures should be carried past the anal region into the skin of the perineum. This is important because after the sphincter ani has been approximated, the anal and rectal walls turn in and difficulty will be found in approximating the lower perineal skin. A continuous suture may be used.

The rectal wall is now intact. The sphincter ani is then grasped with 2 Allis clamps and 1 mattress or figure of eight suture is used to approximate the ends. The same is done for the transverse perinei profundus. The remainder of the procedure is similar to any episiotomy repair. The authors use interrupted or continuous sutures in the muscle, continuous sutures in the fascia, continuous locked sutures in the vaginal mucosa and a continuous subcuticular stitch in the skin of the perineum. The tissues should be accurately approximated but without tension. Empty spaces must not be left and all bleeding must be controlled to prevent the formation of a hematoma.

In regard to after care of the perineum the authors recall that most writers on this subject follow the routine of low residue diet, opiates and constipation, followed at a later date with oil retention enemas, accompanied by perineal care and frequent painting with an antiseptic solution. Other authors, few in number, allow the puerperal period to progress as in an uncomplicated delivery, using only perineal care and antiseptic solutions. The authors' treatment or lack of special treatment, more nearly coincides with the latter group. The routine cathartic, usually licorice powder or castor oil, is commonly given in 48 hours after delivery. Perineal care is given following defecation and one more time during the day. Actually, the only deviation from the normal puerperal routine is the use of enemas. If they are indicated, they are given only with extreme care and with reluctance. There was at least 1 patient in the series, who the authors felt developed a rectovaginal fistula because the enema was given without care.

There were 93 patients who had some kind of complication, or 13.09 per cent. Thirty of these the authors do not consider to be of serious nature, namely, skin separation (3.25 per cent) and edema (0.98 per cent). There were, however, 63 patients or 8.87 per cent who had what the authors consider a serious complication. There was mild skin separation with infection in 2.53 per cent, a sinus from the vagina to the perineal body in 1.98 per cent and a breakdown of the incision

In most of Miles' 547 cases, the forceps were used as an elective procedure to rotate and deliver the head as soon as or shortly after full dilatation was obtained. To my knowledge Miles has been using the Kielland forceps for over 20 years and in his skilled hands I am sure that the results are excellent as his fetal mortality figures attest. Nevertheless I am equally certain that in the hands of the average man, and I refer here to the average specialist, the results both for mother and child will be ever so much better if the forces of nature are allowed to rotate the head and bring it down to the perineal floor.—Ed.)

A STUDY OF 710 COMPLETE LACERATIONS FOLLOWING CENTRAL EPISIOTOMY

D. Frank Kaltreider and D. McClelland Dixon

Department of Obstetrics, University of Maryland Medical School; and the Baltimore City Hospitals, Baltimore, Maryland

The rectal lacerations sustained at the University Hospital, Baltimore, Maryland, from 1935–1946, and the Baltimore City Hospitals from 1938–1946 form the basis for this study. During that period there were 43,503 deliveries at these 2 institutions. There were 15,167 central episiotomies performed, an incidence of 34.86 per cent. In these 15,167 central episiotomies there were 710 third degree lacerations, an incidence of 4.49 per cent. During the same period there were 59 spontaneous rectal lacerations without episiotomy, 0.25 per cent.

As one would expect, 98.82 per cent of these lacerations were in primigravidous patients; 6.4 per cent occurred at the time of second deliveries, while 0.7 per cent took place in patients of greater parity. Ninety-eight per cent of all patients delivered in the authors' clinic from an occiput-posterior or transverse position of the occiput had a central episiotomy. The total incidence of these 2 positions in rectal lacerations was 5 times the incidence in the clinic as a whole. The occiput-posterior as such seems to be the greatest offender since it was found in 16 per cent of rectal lacerations and in only 2.5 per cent of the entire series. Breech extractions do not seem to be a factor. Most authors recommend in delivering a breech that a wide and deep episiotomy be made. The teaching in this clinic evolves from the dictum that in order to use the suboccipito-bregmatic diameter of the head during delivery of a breech, the flexion of the head must be made while the occiput is still inside the pelvic cavity and behind the symphysis pubis. This will probably explain the low incidence of extensions of the perineum in this group of patients. In 17.36 per cent of the patients with rectal lacerations prolonged labor was present. This is 4 times the clinic rate, which may represent an increased incidence of the more difficult type of delivery. More trauma to all the soft tissues is usually obtained in the more difficult delivery; the tissues of the pelvis and perineum become more friable and congested with prolonged labor, and

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yield third degree lacerations with the same frequency, they are drawing this conclusion, if I am not mistaken, from just such an experience; and although I much prefer median episiotomy for the great majority of cases, I cannot agree with this statement. Indeed, I should think if one clinic were to use 100 per cent median episiotomy and another 100 per cent mediolateral episiotomy, the ratio of third degree lacerations would be of the order of 4 or 5 to 1.

But the important question is: Just how serious is a third degree laceration? Is it so grave an accident as to offset the several advantages of median episiotomy? Back in the days when most babies were born in the home it is understandable that a third degree laceration was a major catastrophe. With poor lighting, inadequate exposure, a skimpy supply of instruments and no assistance, incontinence of feces or a rectovaginal fistula was an inevitable sequela in most cases; and it would require only 3 or 4 such tears to put the good doctor responsible for them pretty well out of business. It is no wonder that in those days a third degree laceration was a stigma and disgrace,—a stigma which is still attached to the accident in the minds of most obstetricians.

The great importance of Kaltreider and Dixon's article is to show in a vast series of cases, managed under modern hospital conditions and in competent hands, that a third degree laceration is by no means a major catastrophe because the end results in some 99 per cent of cases are entirely satisfactory 6 weeks later. If a subsequent operation for rectovaginal fistula is to be regarded as a major catastrophe, this was necessary in only 5 of the 710 complete lacerations. To put it differently, a rectovaginal fistula needed repairing only once in 3055 median episiotomies.

In view of the splendid results reported, it might be supposed that the authors would recommend 100 per cent central episiotomy, but they are very judicious about this and state that it may be wise to teach the use of another type of episiotomy (presumably mediolateral) when handling occiput-posterior and transverse positions until experience has been gained. Our results at the Johns Hopkins Hospital with median episiotomy in breech presentation, and with large babies, have been different from those of Kaltreider and Dixon in that our figures show a decidedly higher incidence of third degree lacerations in these 2 groups. It would be my feeling accordingly that they, along with occiput posterior, might well be managed by mediolateral episiotomy. Even with these reservations, it is still possible to agree with the authors that central episiotomy is a most satisfactory procedure in 9 out of 10 deliveries.—Ed.)

PELVIC DELIVERY FOLLOWING CESAREAN SECTION

DANIEL H. HINDMAN

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Although there are increasing numbers of pregnant women, free from pelvic contraction and deformity, who have previously been subjected to cesarean section for some temporary consideration, little has been reported about pelvic delivery following cesarean section.

At Boston Lying-In Hospital, 1928–1946 inclusive, there were 177 vaginal deliveries in 118 patients who had previously been subjected to cesarean. Of these, 41 were delivered twice or more subsequent to hysterotomy. There has

down to the sphincter but not involving it or the rectum in 2.11 per cent. Three of these breakdowns were secondarily repaired successfully on the 10th, 11th and 23rd days respectively. The most serious complication, rectovaginal fistula, occurred in 16 patients or in 2.25 per cent. Most of these complications underwent spontaneous restitution to the normal status within 6 weeks after delivery including all cases of skin separation with infection, all cases of edema and all cases of sinus into the perineum. Of the 16 rectovaginal fistulas 10 healed spontaneously, 1 patient did not return and 5 underwent subsequent operation with ultimate cure of the fistula.

In conclusion the authors review the several advantages of median over mediolateral episiotomies and make the statement that in so far as rectal lacerations are concerned the incidence of this complication is the same in both types of episiotomy. They feel, however, that it is probably advisable not to use median episiotomy when handling occiput-posterior and occiput-transverse positions until experience is gained in the use of central episiotomy. In their opinion median episiotomy is a satisfactory procedure in 93 per cent of deliveries, depending upon the length of experience with the operation.

(The most frequently performed operations in obstetrics are: cutting and tying the umbilical cord, and episiotomy and repair. In regard to management of the cord, as simple as this may seem, it has been the subject of many articles including a number which have recommended this or that type of umbilical clamp. Contrariwise, episiotomy and repair, despite the greater magnitude of the procedure and the greater likelihood of complications, is rarely discussed in our journals. The above paper, in fact, is the first article ever to be written on central episiotomy, I believe, and one of the very few to appear in the last decade or two on any phase of episiotomy. Yet there are many moot questions about the operation which call for discussion and it is high time that they be threshed out.

As I see it, the advantages of median episiotomy are several and may be enumerated as follows: it is easier to repair; faulty healing is very uncommon; it is less painful in the puerperium, indeed, usually painless; dyspareunia rarely follows and the anatomical end results are almost always excellent. In all these 5 respects median episiotomy is superior to mediolateral, at least in my experience.

Turning now to the advantages of mediolateral episiotomy, there seems to me to be only one, but a very important one, namely: whereas in median episiotomy the likelihood of 3rd degree extension is of the order of 3 per cent (depending on operator), the probability of 3rd degree extension with a mediolateral episiotomy is less than 1 per cent. This statement is based on figures compiled in our own clinic a few years ago as follows: in 998 median episiotomies there were 31 third degree tears or 3.1 per cent, whereas in 1420 mediolateral episiotomies only 8 third degree tears occurred or 0.6 per cent. During the past 2 years we have been employing median episiotomy to a greater extent, that is, using it more and more in cases in which we would formerly have employed mediolateral episiotomy. The result in third degree tears following median episiotomy has been much as might be expected, that is, an increase in incidence to above 4 per cent, or a figure similar to that which the above authors report. Meanwhile, our third degree extensions in mediolateral episiotomy have likewise increased to a figure in the neighborhood of 3 per cent. With a little thought these results also might have been anticipated because the more median episiotomy is employed (short of 100 per cent), the more mediolateral episiotomy is reserved for cases in which third degree extension is extremely likely. When mediolateral episiotomy is used only in these dire cases, the incidence of third degree lacerations is bound to be inordinately high and it is manifestly unfair to evaluate the general likelihood of its yielding complete tears on any such basis. When the authors state that the two types of episiotomy

lochia, or serum, where there has been no infection, the incision heals by complete muscular regeneration in 80–90 per cent of the cases; and the other group doubting that the reparative processes could occur without fibrous tissue formation. Schwartz and Paddock appear to have settled the issue in their exhaustive histological study (Am. J. Obst. & Gynec., 10: 153, 1925), concluding that muscle regeneration plays no important role in the healing of the scar and that fibroplastic proliferation was practically normal. In a corroborative study on uteri from pregnant rabbits, they demonstrated the proliferation of fibroblasts along the line of incision entering the interstices between the adjacent muscle bundles. As the scar contracts, this becomes less perceptible. It is this marked shrinking of the newly developed connective tissue and its branching penetration among the muscle fasciculi that make the cesarean scar so frequently invisible at a subsequent operation. Other experimenters with guinea pigs and cats noted that, with increasing stress on strips of uterine muscle containing a scar, rupture occurred not at the site of the old incision but in the neighboring myometrium.

Before adoption of the principles of suturing the incised uterus, the incidence of rupture of the classical incision in a subsequent pregnancy was 50 per cent. Since Sanger introduced the principles of suturing, the incidence reported has varied from 2 to 6 per cent, with a generally accepted average of 4 per cent. A recent report on 3300 cases gives an incidence of 1.5 per cent, and with continued improvement in surgical technique and asepsis, a progressive decrease in the frequency of ruptured scars may be expected.

Statistics on rupture following low-flap cesarean sections may well reflect the results of surgical advances, in addition to the presence of the scar in the noncontractile portion of the uterus. The incidence of ruptures subsequent to cervical hysterotomy has been reported as 0.28–0.25 per cent.

Disruption of cesarean scars forms approximately 20 per cent of all uterine ruptures, but is accompanied by a less formidable maternal mortality (10–15 per cent) than rupture in which a scar is not implicated. The fetal mortality, however, ranges from 70 to 100 per cent.

The present author reports 8 cases of ruptured cesarean scars (7 of them classical incisions). Only 2 occurred in patients selected for prospective pelvic delivery, and only 1 of these experienced labor, the other suffering spontaneous rupture before the onset of uterine contractions. The remaining 6 disruptions occurred without labor prior to the appointed date of repeat hysterotomy, customarily 1 week prior to expected date of confinement. Reports in the literature indicate that such disruption may occur at any stage of gestation and that over ¼ of cesarean scars which rupture separate at 38 weeks or earlier.

When the incision has been sutured carefully with attention to the coaptation of the margins and avoidance of muscle infarction, and when there has been no subsequent infection, one may expect the scar to withstand pregnancy and labor. Many have emphasized that placental implantation over the scar predisposes to rupture. This factor may also help account for the lower incidence of disruption of the cervical scar.

Such pregnancies, deliveries and labors should be directed by well-trained

been a rising incidence of such cases in the more recent years, and at the same time a definite though slight decline in the frequency of hysterotomy—a trend attributable to the adoption and wider use of x-ray pelvimetry during the course of labor in cases of mild pelvic contraction and uterine inertia, enabling the more intelligent interpretation of progress during labor, and also to the greater consideration directed toward successful pelvic delivery following hysterotomy.

Seventy per cent of these patients were delivered by forceps application after full dilatation of the cervix to avoid the expulsive stage, thereby minimizing the stress upon the uterine cicatrix.

Among the total deliveries, 38 per cent concluded the 2nd pregnancy in patients whose 1st pregnancy was terminated by hysterotomy, so that for all practical purposes this group was subjected to what should be considered as a primiparous labor excluding the 2nd stage. No disastrous sequelae resulted. The average duration of labor was 9 hours 25 minutes—for deliveries through the primiparous cervix, a range from 4 to 60 hours, averaging 14 hours 20 minutes, and for multiparas $\frac{1}{2}$ hour to 36 hours, with an average of 6 hours 21 minutes. The frequent elimination of the 2nd stage helps reduce the average. The classical type of cesarean section had been previously done in 56 per cent of the patients (59 per cent of deliveries) and the low transverse type (Kerr) in 20 per cent, the others falling in varied categories or unknown.

The most frequent indication for previous cesarean section had been placenta previa. Premature separation of the placenta, uterine inertia, and cephalopelvic disproportion were the other chief indications. Many of the cases of cephalopelvic disproportion were sectioned elsewhere or were delivered of infants considerably smaller than those for which they had been subjected to operation. It is most unfortunate that hydrocephalus, chorea, or elderly primiparity should ever appear in any roll of indications for cesarean section.

Although the uterus was explored manually in 112 cases, only 4 patients in the entire group had a febrile convalescence, all of them mild—1 mild sapremia in a patient whose uterus was not explored, another in a woman who entered the hospital 2 days following spontaneous rupture of the membranes, and 2 cases of cystitis of 2-days duration. The average hospital stay compared favorably with the general hospital population. There was 1 maternal death (0.56 per cent), occurring in 1932, from aspiration pneumonitis.

All but 6 of the infants were discharged in good condition. There were 5 stillbirths with various causes and 1 death from erythroblastosis.

The fundamental hazard in pelvic delivery following previous section relates to the uterine scar, whether it is firm enough to withstand the distention of the uterus as pregnancy advances and the stress of labor. The functional strength of the scar depends on the histology of wound healing in the uterus and the location of the incision. A number of authors in the past 30 years have reported the difficulty in identifying old cesarean scars, both classical and lower segment, and have studied tissue from scar sites. Two schools of thought grew up: 1 group convinced that in those cases where there has been perfect coaptation of the incised tissues, where the various layers have not been separated by blood clot,

operation (skin incision extending above umbilicus) a repeat cesarean is always employed on the grounds that these high scars rupture more easily; (3) if there is the slightest degree of pelvic contraction abdominal delivery is effected; (4) twin pregnancy always calls for abdominal delivery following a previous cesarean section unless possibly labor should start in 2 months or more before term. These indications seem to us definite and well justified. If none of these conditions is present we weigh in the balance several other factors without necessarily considering any one of them as demanding cesarean section but evaluating them simply as conditions which point to the desirability of abdominal delivery. One of them may outweigh the rest of the group, such as the presence of a very small baby. These factors listed in what seems to me the order of their importance are: (1) a large intrauterine mass such as a large baby or hydramnios; (2) a faulty presentation such as a breech; (3) no previous vaginal delivery; (4) prior operation done in an unknown hospital by an unknown operator,—but quite a few of our own scars have ruptured; (5) febrile puerperium following previous section, but this is not as dependable one way or another as we used to think. A few years ago one of our patients had a perfect, completely afebrile puerperium, yet in her subsequent pregnancy the scar ruptured spontaneously 3 weeks before term while she was sitting placidly in the outpatient department.

Certain other factors which have been stressed a great deal as reasons for repeat sections have not impressed us greatly. For instance, pain in the scar may be very misleading as a sign of threatened rupture. While it may be due to this cause, it is usually the result of adhesions. The same holds true for tenderness. In our experience anterior placentas have given rise to no more ruptures than posterior and we pay no attention to this fact. We do not consider low classical section as a reason for subsequent abdominal delivery but regard labors after low cervical section with more equanimity,—if "equanimity" can ever be maintained in following such a labor. The history of a previous intervening vaginal delivery since the cesarean section is likely to give a false sense of security and little attention should be paid to it. One of our patients ruptured the old scar following 3 intervening vaginal deliveries.

Because of the unpredictability of what is going to happen to these scars and the high cost of rupture, we should limit initial cesarean sections as much as possible. For the same reasons it is understandable that many obstetricians routinely repeat the cesarean section. However, even they will not prevent all ruptures by this means since the percentage of these accidents which occur in pregnancy 2 or 3 weeks before term is substantial,—30 to 40 per cent. With the policy outlined above our results in 624 pregnancies following 1 or more cesarean sections have been as follows (Delfs and Eastman, Rupture of the Uterus, Canad. M. A. J., 52: 376-381, 1945):

Incidence of Rupture of Cesarean Section Scar in Patients under our Surveillance, Who Had Had One or More Abdominal Deliveries

	No.	%
Total deliveries	624	
Cesarean section because of disproportion plus scar	316	50.7
Cesarean section—scar only indication	120	19.2
Delivered vaginally	188	30.1
Total pregnancies	624	
Ruptures in pregnancy	6	1.0
Total labors	188	
Ruptures in labor	2	1.1

obstetricians and conducted in thoroughly equipped maternity hospitals, preferably in patients previously sectioned in one's own clinic and known to have had an uneventful convalescence (only about ½ of the patients reported here had been operated upon in the author's clinic). The patients should be encouraged to seek prenatal care early, and should be early acquainted with signs of rupture and urged to report promptly any symptoms. Blood typing should also be done early. Soft tissue roentgenograms may be useful if they show thinning of the uterine wall; only positive findings of this nature would be of value.

The patient must be impressed with the significance of entering the hospital at the very onset of labor, rupture of the membranes, or appearance of show. Only by uninterrupted, close observation during labor can the earliest signs of impending rupture be detected. Unless blood bank facilities are available, a donor should accompany the patient to the hospital and remain until the end of delivery. If labor progresses satisfactorily, favorable termination may be expected; severe uterine inertia may be a factor for a repeat section. The use of pituitary preparations during such labors is unequivocally censored.

As mentioned before, the 2nd stage of labor is eliminated by effecting delivery by low forceps operation at full dilatation of the cervix. Following delivery, the placenta is permitted to separate spontaneously. When the placenta has been expressed, the accoucher dons a fresh sterile gown and gloves, while the perineum is prepared anew and redraped. The entire gloved hand is placed within the uterine cavity to permit palpation of all portions of the uterus, including fundus and lower segment. Most lower segment scars are indistinguishable, while a furrow or cleft can almost invariably be palpated underlying the classical scar. The examining fingers are pressed firmly against the inner surface of the uterus by counter-pressure of the external hand and are guided over all surfaces in 4 directions and repeated again at the suspected site of the scar: from above, downward; from below, upward; from left to right, and from right to left. Systematic exploration is necessary to detect any small oblique ruptures. Only when the integrity of the uterus has been established beyond doubt may both the pituitary and ergot preparations be administered, even though there is a slight increase in blood loss as a result of the delay.

It is concluded that in properly selected cases previously sectioned for some temporary indication, attempts at pelvic delivery, with the foregoing precautions, are to be encouraged. A reduction in frequency of cesarean section, reduction in maternal mortality and morbidity, and a conservation of hospital days may consequently be expected. 11 tables.

(The management of the gravida who has had a previous cesarean section on nonpelvic indications continues to be a frequent and troublesome problem,—"frequent" for the obvious reason that more and more women have been subjected to abdominal delivery in recent years, and "troublesome" because the behavior of these scars is so unpredictable. Our management of these cases is similar to that of Hindman, that is, vaginal delivery for a selected group, but the criteria upon which we make the selection are not as clear-cut and satisfying as we should like to have them.

Our policy, for better or worse, is as follows: (1) If a patient has had 2 or more cesareans we always carry out abdominal delivery; (2) If a high fundal incision was made in the prior

in length and the thickness of the little finger. It was dark purple in color, of hard consistency and was obviously made up of thrombotic varices. The vaginal mucous membrane was grossly swollen. Everywhere on its walls, up to the upper part of the vagina, varicosities of the thickness of the little finger and less were present. The pedicle of the tumor was ligatured with a transfixed suture and the mass of varicose veins removed. However, the suture holes of the needle gave rise to copious bleeding which proved difficult to control as each new stitch resulted in more hemorrhage. After several attempts, however, it was possible to control the bleeding. In view of this experience, together with the reports in the literature, an elective cesarean section was done at term. The patient developed thrombophlebitis in the puerperium but with heparin and dicumarol therapy she recovered promptly and was discharged 12 days after the operation.

The author believes that since extensive vaginal varicosities in pregnancy often result in profuse hemorrhage, it is valuable in many cases to consider cesarean section as the method of choice for delivery.

(As the author points out, varicosities of the vagina and cervix are fortunately rare. In the one clear-cut case I have seen in recent years, an elective section was done. On the other hand, varicosities of the vulva rarely call for abdominal delivery.—Ed.)

CURARE IN CESAREAN SECTION

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The problem of obtaining adequate relaxation in cesarean section is ordinarily not a difficult one, but occasionally excessive amounts of the anesthetic agent are required to attain this goal. This may be due to our hesitancy to medicate patients adequately prior to cesarean section, in order to avoid the severe depression of the baby which often follows the ordinary use of preoperative drugs before inhalation anesthesia. When sedation is delayed until after delivery, the additional amount of inhalation anesthesia required may also frequently result in considerable fetal depression. To circumvent this difficulty, curare (Intocostrin-Squibb) has been used in conjunction with various anesthetic agents in 285 cesarean sections, in an effort to decrease the amount of the anesthetic drug.

In most instances curare was used in conjunction with cyclopropane or cyclopropane and ether. A variety of other anesthetic agents, including nitrous oxide, pentothal, metopryl, propethylene and trichlorethylene, were used in a limited number of cases, but they appeared to offer no advantage over cyclopropane and ether. In 4 poor risk cases, curare was used twice with local anesthesia and was used in the other 2 cases without supplement. It was the experience of the authors that the best results were obtained when sufficient curare was ad-

A RARE INDICATION FOR CESAREAN SECTION: THROMBOTIC VARICOSITIES IN THE VAGINA

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Whereas varicosities of the leg and vulva are common in pregnancy, varicosities in the vagina and cervix are relatively rare. However, because of the extremely serious complications which varicosities of this kind cause during pregnancy and delivery, a substantial number of cases are on record. Thus, Frank in 1922, was able to collect from the literature 54 cases (Gynecological and Obstetrical Pathology. Gynecological and Obstetrical Monographs, Appleton & Company, New York, 1922, p. 137). The mortality rates in the several series of cases reported are extremely high and individual case histories indicate that danger from fatal hemorrhage is imminent, not only during labor but even in the latter weeks of pregnancy. Thus, in the study by Frank, the maternal death rate was estimated as 60 per cent. Since the vaginal wall overlying varicosities becomes thinned out, such veins may be ruptured by the slightest trauma and profuse bleeding from this source has been reported following sexual intercourse, internal examination and uterine curettage. During the last month of pregnancy hemorrhages from varicosities have often been observed resulting from slight exertions or even with apparently no cause. Sometimes the bleeding is insignificant at first, but mostly, however, is very profuse from the onset. Stoeckel states that in his case the patient lost 1200 cc. of blood from her varix at the back wall of the vagina in less than a minute. If vaginal varicosities can thus start bleeding profusely without any specific cause, it is obvious that delivery or interference by way of the vagina may prove fatal. In a case reported by Wieloch the patient died of hemorrhage after delivery in the course of 3 hours; a postmortem examination showed that the hemorrhage originated from varicose veins in the cervix. Especially when the varicosities form a special tumor the danger of rupture is extremely great as it constitutes an obstacle interfering with the passage of the infant.

If the varix bleeds, immediate attempts must be made at stanching the bleeding. The suture must be made by means of a needle above and below the bleeding point. A varix with a pedicle can of course be ligatured and removed by operation. However, as many of the reported cases show, the placing of the suture is by no means easy. As the difficulties in stanching a hemorrhage once it has begun are great, there is a growing tendency to favor cesarean section in good time as the method of delivery in these cases.

The case of a 31 year old woman is reported who, during her previous pregnancy, had had varicosities in the legs and during her present pregnancy was discovered to present a tumor protruding from the vulva. The tumor was attached to the posterior wall of the vagina by means of a pedicle of about 2 cm.

intravenous infusion of glucose solution was begun, the infusion providing a ready means of administering the curare. In most cases, curare was given in 20 unit doses every 3 to 5 minutes until definite respiratory depression occurred. Usually 1 or 2 doses of the drug were given before the cyclopropane was started. Another method, which was found to be more convenient in some cases, was to give 40 to 60 units of curare intramuscularly upon the arrival of the patient in surgery, then supplementary doses of 20 units intravenously as required. The total dosage was the same for both methods. Inhalation anesthesia was withheld until the abdominal skin preparation was begun, and then only sufficient anesthesia was given to prevent muscular movement until after the delivery of the baby. It was found to be desirable to give a small amount of ether, usually 10 to 20 cc., to prevent the patient from completely reacting before being returned to her room.

Curare did not produce any unusual effects on the mother. The muscle tone of the uterus was not altered and there was no increase in uterine hemorrhage. In those cases in which there was reason to believe that vomiting might occur, an endotracheal airway was inserted to prevent aspiration of vomitus after the curare effect had been obtained. This is usually accomplished during relatively light anesthesia because of the relaxation afforded by the curare. It has been our impression that curare is very well tolerated even in poor risk patients. Hemorrhage and debility have not proved to be contraindications in the use of this method of anesthesia. Cases of toxemia of pregnancy have not been aggravated by curare. When convulsions have been present with toxemia they could be minimized but not always completely controlled by ordinary doses of curare. The use of this drug has not appeared to alter the course of the toxemia. Patients having severe toxemia and convulsions probably receive greater benefit from carefully administered caudal or spinal anesthesia.

(The use of curare in cesarean section, through this substantial series reported by Whitacre and Fisher, takes its place among the advances in anesthesia technics designed to protect the baby from overwhelming transplacental narcosis. Thus, it would seem that the skillful administration of curare in cesarean section materially diminished the amount of a variety of general anesthetics required to deliver the baby. It is significant that this study in humans confirms the investigation of Harroun and Beckert in dogs, which postulated that the placenta acted as a barrier in preventing transmission of curare from the maternal to the fetal blood stream.

It should be emphasized, however, that the use of this powerful conduction block of the myo-neural junction places squarely a new responsibility upon the obstetrician-anesthesiologist team; namely, that of maintaining adequate oxygenation of both mother and baby during operation and for the immediate hours in the postoperative period. *Mortality has occurred and will continue to occur when this technic is used carelessly and by those untrained in the altered pharmacodynamics involved.*

For patients undergoing cesarean section with toxemia, respiratory, cardiac, or metabolic disease, or for those delivering premature babies, it appears that the continuous conduction nerve block procedures are most advantageous to both mothers and babies. In those cases falling definitely in the poor risk group where there has been hemorrhage from premature separation of the placenta or from placenta previa, and in those cases with profound anemia and hypotension, it would appear that the judicious use of curare with light general anesthesia may become the anesthetic technic of choice.—Robert A. Hingson)

ministered to permit the use of only minimal amounts of general anesthetic prior to delivery.   The ability to reduce the concentration of the anesthetic in the mother resulted in a corresponding decrease in the incidence of severe fetal depression.   When curare was used alone or with local anesthesia, there was a tendency toward the occurrence of muscular spasm, including bronchial spasm and excess salivation.

The authors have encountered no cases in which curare could be considered a factor in causing fetal depression.   Amounts of curare up to 200 units have not, in the authors' experience, produced any undesirable effects upon the baby.   The absence of a curare effect upon the child does not appear to be due to an unusual resistance of the newborn to the drug, since they frequently observed the effectiveness of small doses of curare in very young babies.   It would seem that the placenta must act as a barrier and prevent transmission of curare from the maternal to the fetal blood stream.   Harroun and Beckert (Surg., Gynec. & Obst. 84: 491, 1947) reported some experimental work on dogs which appears to confirm this impression.   The incidence and degree of respiratory depression in the baby were somewhat greater with curare and cyclopropane than when regional or spinal anesthesia was used; however, they were not sufficiently greater to be of real disadvantage.   The incidence and degree of fetal depression with curare-cyclopropane anesthesia have been less than with cyclopropane or ether anesthesia.   In 70 per cent of the cases, no resuscitative efforts, except simple aspiration of the upper respiratory passages, were required.   Slight depression occurred in 17 per cent of the babies.   In these cases, in addition to aspiration of the pharynx, the lungs were gently inflated with oxygen after one minute.   Tracheal aspiration was rarely required.   All babies in this group had good muscle tone and responded promptly to the administration of oxygen.   Respiratory efforts of the baby sometimes started before the head was delivered, causing occasionally a secondary depression from aspiration of large amounts of foreign material.   The same difficulty, however, has been encountered with patients having regional or spinal anesthesia, where there is no respiratory depression of the baby.   Two babies, or 0.7 per cent of the total number, were severely depressed.   Here, in addition to the above resuscitation measures, an endotracheal tube was passed under direct vision to aspirate foreign matter from the lower respiratory tract and to institute artificial respiration.   In both babies, respiration was established after a short time and recovery occurred.   However, these babies did not have good muscular tone on delivery.   Both mothers had received sufficient preoperative medication and general anesthesia to account for the degree of the depression.   The incidence of stillbirths was 5.5 per cent, but in these cases there was no positive evidence of fetal life prior to delivery.

The amount of curare used in this series varied from 40 to 200 units, the usual dose being 100 units.   Since some patients require considerably less or more than the average amount of drug, it would sound advisable to administer the curare in divided doses.   Routinely the patients received 0.1 gram of pentobarbital sodium and 0.4 mg. scopolamine 1 hour before operation.   Ten to 15 mg. of morphine was given at the time of delivery.   Prior to the induction of anesthesia an

Cause of Death. Eclampsia, postpartum from available data. Complete autopsy might have revealed cerebral hemorrhage, but the death still would have to be ascribed to eclamptic toxemia.

Preventability of Death. Definitely preventable.

Responsibility of Death. Physician.

COMMENT

Any criticism leveled at the late prenatal care and care in labor and the puerperium is amply justified and cannot be too severe. What toxemia signs or symptoms the physician was awaiting before the conscientious or rigorous institution of toxemia work-up and therapy cannot be guessed. The incomplete patient study at the first prenatal visit is regrettable but not contributory and its negligence nowhere near as glaring as the errors of omission beginning with the 33rd week of gestation. Prenatal follow-up visits as much as 30 days apart can hardly be declared as ample. This is most certainly true when, as at 33 weeks gestation, proteinuria and edema are found after excess weight gain. There can be no justification for allowing another 6 weeks to go by before seeing the patient. The second serious omission occurred at the time of the house call 1 week before the estimated date of confinement. Here, the physician had a golden opportunity to rectify the lethargy of the previous 6 weeks but this opportunity was cast to the winds. Hospital admission with adequate patient study and rigorous toxemia therapy would almost certainly have guaranteed a less unfortunate outcome. Instead of this, the patient was left at home with apparently unsupervised suggestions for toxemia therapy, the value of which were as near to nil as possible. These 7 days were valuable ones not utilized. Finally, the case was still not lost when the patient was admitted in advanced labor and safely delivered. Instead of at long last trying to correct the errors of 2 months' standing, the patient was sent from delivery room to ward and allowed to go untreated, undiagnosed, i.e., so far as the toxemia is concerned, until her end was almost in sight. The pitocin may have been a contributory factor in pushing the severe preeclamptic state over into eclampsia which may well have produced a cerebral accident which may have been the immediate cause of death. All these errors are so contrary to modern obstetrics, so archaic, that when the physician was finally confronted with eclampsia and prompt death, many nights of insomnia from a hounding guilty conscience should have resulted. The autopsy would have confirmed the toxemia, but examination of the cranial contents would have been of great interest to determine whether cerebral hemorrhage was the direct cause of the prompt exitus.

CASE NO. 65

The patient was a 31 year old colored registered para 3-0-0-1 with an incompletely measured pelvis, negative blood Wassermann and Kahn, undetermined Rh factor, whose last menstrual period began on January 17, 1946, making her estimated date of confinement October 24, 1946. The hospital record is grossly incomplete and much of the following information was derived from the attending physician's memory.

The family history is noncontributory although the mother is said to have succumbed at 30 years from "acute indigestion and pregnancy." The past general history reveals a

Maternal Mortality Reports

(Secretaries of Maternal Mortality Committees are invited to submit selected cases of maternal deaths, with analyses appended, for publication in this section of the Survey. Cases should be chosen on the basis of educational value, not because of rarity. For obvious reasons complete anonymity will be maintained.

Readers should note that the comment which follows each case history represents the opinion of the Committee concerned and does not necessarily reflect the attitude of the Editors.)

CASE NO. 64

The patient was a 26 year old registered colored para 1-0-1-1 with a negative blood Wassermann, unknown Rh factor and unmeasured pelvis, whose last menstrual period began January 14, 1946, making her estimated date of confinement October 21, 1946. Nothing is known of her past or family history. The only facts known about the previous pregnancies are that the first, 7 years ago, was carried to term and produced a living child while the second terminated in abortion at 3 months about 2 years after the first.

She presented herself to her family physician for prenatal care in the 16th week of gestation. Pelvic mensuration is said to have been done and the pelvis declared normal, but no measurements are submitted to substantiate this claim. No routine blood study of Rh determination was done. Organs examined are said to have been normal. Follow-up prenatal examinations were apparently adequate but rather infrequent, never being closer together than 30 days with the last 2 visits 6 weeks apart. The pregnancy is presumed to have progressed normally except for excess weight gain, i.e., 9 pounds between the 20th and 25th weeks. However, when last seen at the office, a 2-plus proteinuria is recorded and she presented edema of the feet. This was at 33 weeks' gestation and epsom salts, limitation of fluids and a salt free diet were prescribed. These rather early toxemia signs should have demanded an early check-up visit but the patient was not seen again until 6 weeks later, i.e., 1 week prior to her estimated date of confinement. This visit was a house call and may have been in response to severe toxemia symptoms—generalized edema and headaches in particular. The blood pressure was found to be 200/110; no urine was obtained for analysis and no weight determined. A diet of fruit juice and water was prescribed as well as urotropin and acid sodium phosphate, bed rest and an ice bag for her head. No attempt was made to hospitalize the patient but she was told that if improvement did not follow, labor would be induced.

The patient was not seen again until 1 week later when she was admitted to the hospital in advanced labor. The labor was precipitate with only 2 hours of labor prior to admission and delivery approximately 20 minutes later. Morphine and atropine were given upon hospitalization and delivery was spontaneous without anesthesia. Pitocin was given after delivery of the placenta. She is said to have been in good condition upon being returned to her room but this is pure objective observation. It is noteworthy to record that no admission examination was performed, no blood pressure taken and no urinalysis done after admission; in fact, nothing to evaluate the degree of toxemia or to treat it. The subsequent course should, then, not have come as a surprise but should have been anticipated.

Eight hours after delivery the patient had 1 eclamptic convulsion from which she never rallied but succumbed 2 hours later. Sedation begun after the convulsion, as well as other therapy for the toxemia, was not only long overdue but also homeopathic in nature (nembutal via rectal suppository). Last minute heroic therapy was of no avail. Autopsy was not performed, not requested because of the absence of an autopsy room at this hospital. The child was delivered in good condition, weighing 7 lbs. 2 oz., and survived.

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was magnesium sulfate (twice i.v. and once i.m.) and morphine sulfate on 2 occasions, although there is an off-the-record statement that 10 per cent glucose in Ringer's solution was given every 8 hours and ¼ gr. morphine every 6 hours. Uterine contractions were poor and infrequent. Note that on the second hospital day, this severe toxemia patient was given 4 minims of pituitrin as a single dose intramuscularly to stimulate labor. On this same day, according to the physician's memory, intrapartum fever appeared and was treated with penicillin. Mention of the incompleteness of this hospital record must again be emphasized in noting that the temperature, pulse and respiratory rates do not appear at any time.

Whether this patient ever completed the first stage of labor is not known. However, after approximately 40 hours of labor she was anesthetized with ether and the physician attempted a podalic version but failed, and a second physician attempted it and failed again to locate the fetal feet. Now for the first time cephalopelvic disproportion was suspected. The anesthetic was discontinued and labor allowed to continue. Curbstone type of consultation was obtained from 5 fellow general practitioners, i.e., nothing recorded of findings or advice. It is said that cesarean section was considered but not carried out on account of "the condition of the patient." Apparently version and extraction was agreed upon and this final insult administered in the last 2 hours of life, i.e., the second ether anesthetic was begun 44 hours after the onset of labor, 4 hours after the previous anesthetic was begun, and 45 hours after rupture of membranes. Some one of the 6 physicians did eventually effect version with the bringing down of 1 foot. That the fetus was of excessive size is attested to by the fact that its ankle is said to have been as large as that of the wrist of the physician. After 1¾ hours of administration of the second anesthetic and with the patient still undelivered, the first of 2 convulsions began with exitus within 15 minutes from what the physician thought was cerebral hemorrhage.

Cause of Death. Shock produced by an ill-advised operative vaginal delivery under repeated and prolonged ether anesthesia to a patient with intrapartum eclampsia, cephalopelvic disproportion due to an excessive sized fetus and/or contracted pelvis, and with marked obesity.

Preventability of Death. Preventable.

Responsibility for Death. Physician.

<center>COMMENT</center>

In view of this patient's past obstetrical history of prolonged labor, she should have had not only complete pelvic mensuration, but also roentgen pelvimetry. In view of her previous toxemias and toxemia of the final pregnancy, her prenatal follow-up should have been under closer observation, certainly with more frequent check-ups, if not hospitalization for toxemia study when she revealed blood pressure up to 180/120 at 24 weeks' gestation. Care of labor was certainly poorly conducted or supervised. The routine unsterile or semi-sterile vaginal examinations are to be forever condemned. They produced or helped to produce an intrapartum infection which might have produced death if the patient had recovered from the shock and toxemia. From the hospital record and the physician's memory one cannot ascertain the type of toxemia. Certainly she had what was described as typical eclampsia but there is ample evidence to suspect that this was superadded to arteriolosclerosis. Sedation was apparently sparingly given as was glucose. The use of saline solutions to toxemia patients is in as poor taste as the administration of pituitrin, for either is capable of pushing

breast abscess in 1939 (probably in her second puerperium) and purpuric spots over the legs diagnosed as drug rash (aspirin) 2 months prior to her last conception. Her past health is said to have been fair, but there is no diagnosis to substantiate this except for obesity—her average weight is given as 256 pounds and she measured only 5 feet 1 inch in height. Her past obstetrical history was hazardous and characterized by toxemia and prolonged labors. The first is said to have terminated at term in low forceps delivery of a stillborn of unrecorded weight and after a labor of unknown length. She was admitted as an eclamptic, had retention of the placenta (10 hours) and a severe puerperal infection. The second pregnancy was terminated at the same hospital, 1 year later and 1 week before the estimated date of confinement, spontaneously after a 51¼ hour labor. The type of toxemia was not determined but is presumed to have been severe pre-eclampsia with delivery of a living child that succumbed 3 months later to malnutrition. There is no available information on the third pregnancy except that it produced a 6 pound infant which is now alive and 5 years of age.

As previously stated, the last menstrual period for the final pregnancy began on January 17, 1946. She reported to her private physician for prenatal care on April 1, 1946, i.e., 10⅔ weeks after her last menstrual period. She now weighed 283 pounds, had no hypertension and apparently was not ill. The pelvic examination did not include mensuration of the C.D. and only the first estimate of the T.I. The blood study did not include hemoglobin or Rh determinations, i.e., was limited to a determination of the absence of lues. No follow-up or special study was performed because of the marked obesity or previous history of severe toxemias of pregnancy.

Follow-up prenatal visits occurred roughly each month, every 5 weeks on 2 occasions, and she was not seen for 7 weeks after the last prenatal visit. It is claimed that both abdominal palpation and vaginal examination were performed at the time of each visit. The urine is said to have been free of protein bodies throughout the prenatal course. The weight gain was moderately excessive except between the first and second visits when it was more excessive, i.e. 9 pounds in 5 weeks. The blood pressure ranged between unbelievable limits. It was 120/80 at the first visit (10⅔ weeks gestation), 140/100 at the second (16 weeks), 120/80 at the third (21 weeks), 180/120 at the fourth (23 weeks), 150/108 at the fifth (29 weeks), and 120/78 at the last prenatal visit (33 weeks gestation). The only therapy is said to have been low carbohydrate, fat and salt poor diet, with advice to rest and to take salts frequently. The excess weight gain and the intermittent hypertension did not seem to alarm the physician enough to suggest more frequent prenatal visits or special study.

The patient was not seen again until 7½ weeks later, i.e., 2 days after her estimated date of confinement when she was admitted to the hospital, as planned, in labor and approximately 2 hours after spontaneous rupture of membranes, labor having started an hour before admission. She then complained of severe headaches of unspecified duration, nausea with vomiting, and of a swollen face. No urinalysis was done, her blood pressure was 180/140 and she presented marked pitting of the lower extremities and abdominal wall. The position of the fetus could not be ascertained from abdominal palpation due to obesity. A semi-sterile vaginal examination was done by the nurse who found the cervix thick, 3 cm. dilated, and presenting fetal head unengaged. It should here be pointed out that this, as well as subsequent vaginal examinations, were performed, as appears to be the custom in the hospital, with no sterile precautions except for the wearing of a sterile glove, but presumably after shaving of the pubic hairs.

The labor was prolonged (46⅔ hours) and characterized by primary uterine inertia. No rectal examinations were performed to follow the course of labor, but instead the same type of vaginal examinations described above. Four of these are definitely charted, but the record infers that many others were performed. The follow-up study of the toxemia was apparently essentially nil and its therapy inadequate. It appears that no urinalysis or blood study and only 1 blood pressure determination were obtained. According to the hospital record which covered a period of some 45 hours the only toxemia therapy given

week prior to her estimated date of confinement and revealed the fetus presenting by frank breech with the pelvis noted as "normal" and the breech unengaged.

Membranes ruptured spontaneously at term and, though she was not in labor, she was admitted to the hospital. Apparently the only examination done upon admission was that by the nursing staff showing a floating presenting pole, no pains, and a closed cervix. Eighteen hours after admission good labor began and sedation consisted of 1½ grs. seconal and 100 mg. demoral. After approximately 4 hours the cervix was said to have been fully dilated with the presenting breech unengaged. Two minims of pitocin were given to "engage the breech" and she was transferred to the delivery room to be given gas with bearing down encouraged with pains. After another hour the presenting breech was still unengaged. The patient was then anesthetized with cyclopropane and the breech decomposed, bringing down one foot, after which extraction is said to have been effected without difficulty. The newborn weighed 10 pounds 4 ounces, was described as in good condition and survived. The placenta was expressed and a second degree perineal laceration repaired, with an estimated 350 cc. blood loss. There may well have been considerable bleeding for a pack was described as being left in the cervix to aid "in the contraction of the uterus" and the patient promptly sent to her room with the physician apparently leaving the hospital approximately 45 minutes after delivery. It is to be noted with censure that no blood pressure was taken after the nurse's initial admission recording (118/80) until practically terminally. Except for the nurse's recording up to transfer of the patient to the delivery room, this is also true of the pulse rate.

Upon return to her room, the physician says she had aroused from the anesthetic enough to talk with him, had no abnormal bleeding and a firm corpus uteri, apparently in good condition; yet he says that simultaneously she appeared "washed out" and he ordered intravenous 5 per cent glucose. Whether all of this solution had been given within an hour is not stated, but at that time she was found to be in shock. The resident obstetrician recorded her blood pressure as 0/0 and described her uterus firm without the presence of abnormal bleeding. Heroic measures were of no avail. She complained of sudden chest pain and promptly expired. The resident suspects pulmonary embolism but the only conceivable origin of such would be amniotic contents. The family physician returned after the patient's exitus and "did not have the heart" to ask permission for an autopsy. This latter is regretted for that physician thereby eliminated his last chance of absolving himself as responsible for this maternal death. ·In all probability this would not have resulted and instead there would have been a written record of his negligence.

Cause of Death. Shock following excessive blood loss, and/or traumatizing delivery, and/or lacerations of the upper birth canal in delivering an excessive-sized fetus.

Preventability of Death. Preventable.

Responsibility for Death. Attending physician.

<center>COMMENT</center>

This is a sad story and any recollection of it should give the attending physician very little comfort. There were many errors, especially of omission, in her prenatal care but these perhaps had little or nothing to do with contributing to the outcome. The care in labor, delivery, and most particularly in the brief puerperium was faulty and directly contributory if not responsible for the fatality. Physical examination and an admission note would have been helpful in ascertaining the patient's state of health prior to the onset of labor. There was absolutely no need for the intramuscular pitocin at the supposed end of the first stage of labor since the patient is presumed to have had good uterine contractions.

the preeclamptic into the eclamptic state. Ether anesthesia has been shown to produce liver damage analogous to that seen in eclampsia and is therefore on the verboten list for use in toxemia patients, certainly the severe ones. Podalic version with extraction performed many hours after rupture of membranes and drainage of amniotic fluid is a shocking procedure and may produce rupture of the uterus at that late stage unless relaxation of the uterus is possible under deep surgical ether anesthesia. Attempted vaginal delivery with cephalopelvic disproportion is traumatizing and shocking. The disproportion should have been suspected from careful abdominal and pelvic examination and confirmed with the aid of x-ray. It is unfortunate for the patient that competent and adequate consultation was not sought early though the patient was not a good risk for any type of obstetric delivery. However, cesarean section done early or craniotomy late instead of podalic version should not have been as shocking. The incompleteness of certain hospital records is well emphasized here for it materially hampered a thorough analysis of this case. Postmortem examination was not performed, not requested since it is customary to request these only in cases where the diagnosis is obscure, for there are no facilities for autopsy at this hospital and they have to be done by the physician at the undertaker's establishment. However, the cause of death would seem to be clear. No patient, no matter how good an obstetric risk, can withstand repeated traumatizing insults without breaking under the load. The severe toxemia and the marked obesity were certainly major contributory factors in lowering this patient's risk and in producing the unfortunate outcome. The Committee can see no escape from classifying this as a preventable maternal death with clear-cut physician responsibility.

CASE NO. 66

The patient was a registered white private 42 year old para 4-0-1-4 with unmeasured pelvis, unknown blood Wassermann and undetermined Rh factor, whose last menstrual period is said to have begun July 9, 1946, making her estimated date of confinement April 16, 1947.

She appeared for prenatal care at 10 weeks of gestation. Nothing is known of her past obstetrical history except for its numerical value. The family history is not known, menstrual history was not recorded, and the only comment on her past history is that she had had varicose veins of the right leg for some years. Her previous health is said to have been "not good" but this statement is not further substantiated.

At the first prenatal visit a general physical examination is said to have been normal except for the varicosities noted above. Pelvic examination revealed no abnormalities except for a "loose vagina." Pelvic measurements are said to have been normal but nothing is recorded to substantiate this contention. No blood Wassermann, no routine blood counts, and no Rh determination were done at this time or at any later date by her local physician. There were only 7 follow-up prenatal visits, all of which were generally spaced a month apart except for the first which occurred 2 months after the initial visit. These appear to have been complete and revealed no pathology except for a 1+ proteinuria at the last visit—3 days before term and delivery. Total weight gain over the observed period amounted to 21 pounds (from 115 to 136 pounds). Four days before the last office visit she was seen at home because of "influenza" for which penicillin and bed rest were prescribed and from which she apparently recovered promptly. An x-ray was obtained a

On the second hospital day blood chemistry showed moderate retention of protein metabolites (NPN 40 mg. per cent) and moderate reduction in total proteins but no disturbance in A/G ratio though there was reduced albumin content. There was moderate alkalosis (CO_2 combining power of 67 vols. per cent), some reduction in blood chlorides (379 mg. per 100 cc.) and an icterus index of 17 units. The urine showed no bilirubin. It was believed that her hyperemesis was being well controlled but on the following day she claimed not to be able to move her extremities very well, felt weak and was rather apathetic. Urine continued to be free of acetone bodies. On the fourth hospital day she seemed improved with no vomiting and it was believed that her icterus was fading, but the index was later reported as the same as when previously taken. Blood chlorides were now within normal limits and her routine blood count remained unchanged.

On the fifth hospital day she became mentally confused and extremely uncooperative, resisting being taken by stretcher to the x-ray department. She talked wildly and had delusions of persecution. Sodium amytal was given intravenously in order to quiet her and to proceed with routine x-rays of the chest. Temperature climbed gradually and pulse became rapid and weak. Intravenous fluids, especially saline, were given in large amounts when the alkalosis was found to have increased to 86 vols. per cent. Simultaneously the NPN was found to be within normal limits. Urine and routine blood studies remained unchanged but urine culture grew E. coli. Spinal fluid pressure was found to be increased to 285 mm. of water but the fluid was otherwise normal. Glucose was given intravenously for some hours and edema of the jaws appeared as the patient's condition continued to become worse with death about 18 hours after the onset of mental confusion. Adequate supervision and consultation was available after hospitalization.

An autopsy was performed and was complete except that weights and measurements were not performed to confirm deviations from normal sizes of organs. The heart is said to have been normal but the lungs extremely edematous. The liver is described as being small with focal necrosis and fatty degeneration, central lobular in location. The uterus contained a fetus of an 18½ weeks' gestation. There were several myomata, the largest measuring 10 cm. in diameter, which had undergone considerable degeneration. The brain showed generalized edema. The right renal cortex contained numerous small pyemic abscesses. It was the pathologist's opinion that death was due to toxic hepatitis.

Cause of Death. Apparantly acute yellow atrophy of the liver in an elderly primigravida at 18½ weeks' gestation associated with myomata uteri (one degenerating) and pyelonephritis.

Preventability of Death. Preventable.

Responsibility for Death.
a. Patient—failure to seek medical care earlier.
b. Hospital—delay in hospitalization.
c. Physicians—failure to interrupt pregnancy.

<div align="center">COMMENT</div>

It is regretted that after a week's therapy and a complete autopsy, it is not possible to arrive at a clear-cut diagnosis and evaluation of the exact cause of death. The patient must be criticized for waiting 14 weeks with 40 pounds of weight loss before seeking medical care. The hospital must be criticized for not making space for immediate admission of an acutely ill patient. Treatment thereafter would seem to have been along recognized lines and patient study as complete as indicated at the time. It might have been to the advantage of the patient's disease to have had the pregnancy interrupted promptly upon admission

The exact state of the cervix is not known but one must seriously doubt that the cervix was actually fully dilated. If it was, there can be little criticism for having decomposed the breech with delivery by breech extraction. Whether the cervix was actually inspected for lacerations is not known, but the need for a cervical tampon is questioned. The most serious error is the failure to have followed the patient's condition in labor and in the immediate puerperium with pulse rate and blood pressure determinations. Had these been done, there is no doubt that the state of shock would have been more accurately known and could have been properly treated. However, even in the absence of these, the physician was aware of shock and/or hemorrhage as shown by his observation of the washed out appearance and his therapy for it. The worst possible substitute for blood and for treatment of shock or hemorrhage was selected and the patient left to the mercy of the hospital staff and the Lord. It seems incredible that a physician would have the effrontery to depart before the patient was known to be recovering from the known shock. Comments on the failure to request postmortem examination have already been made.

CASE NO. 67

The patient was an unregistered, colored, charity, 37 year old primigravida with negative blood Wassermann, undetermined Rh factor and unmeasured pelvis whose last menstrual period began December 16, 1946, making her estimated date of confinement September 23, 1947. Although eventually she presented for adequate medical care, there are still some phases of the case which are not clear.

Her past health is said to have been good and she worked as a beautician until marriage 2 years ago. There were no past illnesses of note, the menstrual history was normal and the family history was noncontributory.

On April 8, 1947, at 16 weeks of gestation, she presented herself to the outpatient clinic complaining of nausea and vomiting of 14 weeks' duration, with an estimated weight loss of 40 pounds in that period of time. She was seen by the resident in the medical clinic who found the blood pressure to be 98/70, pulse 115 and respirations 20. She appeared chronically ill with dry and wrinkled skin, icteric sclerae, pale conjunctival mucosa, and an enlarged uterus with several myomata as well as a pregnancy. Hyperemesis gravidarum and early hepatic failure were diagnosed. She was then seen by the obstetrical service where no pelvic measurements were obtained and the Rh factor not determined. The urine showed a trace of proteinuria and a few white blood cells. Hospitalization was recommended but not effected until 4 days later.

Upon admission she complained of lower abdominal tenderness and of constipation controlled only by taking salts. She had an unquenchable thirst and had apparently had no recent nausea or vomiting. She claimed that her urine was light in color and stools normal as regards color. Her skin is said to have been hot and dry but temperature was only 98.0°F., with the pulse 100, blood pressure 130/60 and respirations 20. She was lethargic and answered questions slowly. Physical examination revealed essentially the same findings as previously in the outpatient department. The liver was neither palpable nor tender. There was a gross tremor of both hands. Catheterized specimen of urine showed no acetone or diacetic acid, but it was yellow in color and contained a few hyaline casts as well as a small number of both red and white blood cells. She had an obvious anemia with the hemoglobin 8.5 grams with red cell count of 3.37 million and little leucocytosis (11,600). Therapy for hyperemesis was instituted with the administration of intravenous glucose, sedation and vitamins. Much of her caloric intake was per orum because she had little or no nausea or vomiting after admission.

Gynecology

TESTOSTERONE PROPIONATE IN INOPERABLE CARCINOMA

J. WYATT

St. Thomas's Hospital

In Feb., 1945, a 57-year-old woman was admitted with postmenopausal bleeding. There had been frequency of micturition, bearing-down pain and pain in both groins for 2 months. She had lost about 1.8 kg. in weight.

On examination the uterus was enlarged with some fixity and there was thickening in the right broad ligament. Curettage showed a squamous-cell carcinoma. Upon opening the abdomen carcinoma of the uterus was found with extension into other pelvic organs, and the radiotherapist felt that treatment with deep x-rays would be of no value. Therefore, it was decided to try large doses of testosterone propionate.

From March 5th onward, the patient was given 525 mg. the first week, 825 mg. the second and 1,050 mg. the third. The dose was then reduced. From April 16, she received 2 weekly injections of 75 mg. each. By April 24 all vaginal bleeding had ceased and the patient felt little pain. In June there was occasional loss of blood; in September the uterus seemed smaller and more mobile. A curettage in October still showed active carcinoma. After this the loss of blood became daily, so the biweekly dose was doubled to 150 mg. In January there was slight loss once a fortnight and by March the loss increased again and the dosage was raised to 400 mg. a week. The patient gained weight; the pelvic state remained unchanged.

By January, 1947, the uterus was larger and the patient going down hill. Testosterone was continued until March, at which time it was felt to be of no further good. The total dosage was 35,000 mg. The patient died on June 14, but postmortem examination was not performed.

The author felt that the treatment prolonged the patient's life with comparative comfort.

(The earlier endocrine connotations of cancer pertained to the question of the etiology of the latter disease and there were not a few investigators who had the idea that the endocrines might ultimately, as one distinguished pathologist put it, furnish the key to unlock the closed door of cancer. It has been possible in various animals to produce cancer-like lesions with cancer, and in at least one species, the mouse, to produce genuine carcinoma of the cervix. However, even in the latter instance, it has not been possible to eliminate the fundamental or genotypic factor, without which the estrogens would not have produced such cancers, so that the weight of evidence at present indicates that they play only a predispos-

because the hyperemesis had been of long standing and was obviously severe. The impression at the time was that the disease was under control but the disappearing nausea and vomiting gave a false sense of security. Interruption of the pregnancy would have called for a major procedure and this did not seem indicated at the time, especially in the light of the apparent improvement. However, the final outcome would suggest that the patient's life on admission was already so compromised that the end result would have been the same. Finally, it now appears that the diagnosis was erroneous and that this patient died of acute yellow atrophy of the liver. To confuse this disease in the first half of pregnancy with hyperemesis gravidarum is easy. While the autopsy was complete, it is lacking in details of mensuration, especially of the liver, which should have given confirmatory evidence.

implantation technics which have been advocated, especially in the treatment of menopausal symptoms, in which the very thing we should not want is uninterrupted continuance of the estrogens for any great length of time. Oral therapy, on the other hand, permits of ready decrease, increase or discontinuance of the estrogens.

I do not think that most of us have been bothered with poor healing of tissues in plastic procedures, even in old women. Estrogens given in sufficient amount would increase the thickness of the mucosa, but amounts adequate for this would certainly cause uterine bleeding in some cases, aside from increasing the local vascularity of the tissues, as the author himself mentions.—Ed.)

ing rather than primary role in etiology. That this predisposing role is an exceedingly important one in those areas normally under the physiological control of estrogens, the genital tract and the breast, has been accepted since the work of Loeb in 1917.

The interesting endocrine development of recent years in relation to cancer is the application of the sex hormones in the treatment of cancer. The starting point along these lines was the demonstration by Higgins of the value of stilbestrol in the treatment of prostatic cancer. While not curative, the palliative results, especially in the cases associated with bone metastases, have been so striking that the method has achieved general adoption. Other applications of the endocrines have been the use of testosterone in correspondingly late cases of breast cancer, the thus far less striking employment of large doses of estrogen in the same disease, and the advocacy by many of castration in premenopausal breast carcinoma and also in prostatic cancer.

Thus far testosterone has not often been used in the treatment of any form of advanced uterine cancer, so that the good palliative results observed by Wyatt in his one case of inoperable cervical carcinoma are at least suggestive.—Ed.)

PREOPERATIVE IMPLANTATION OF ESTROGENS IN SOME VULVO-VAGINAL OPERATIONS

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The author reports the results achieved with the implantation of estrogenic hormone (estradiol benzoate—20 mg., dinestrol—25 mg. and stilbestrol—40 mg.) in pellets as a preoperative plan of treatment in patients, usually postmenopausal, who were going to be submitted to vulvovaginal operations, especially for genital prolapse. Implantation was carried out in the subcutaneous tissue of the scapular region with the aid of a trocar, usually from 10 to 15 days before the operation.

This procedure was utilized in 18 instances: 17 of prolapse and 1 vesicovaginal fistula. Vaginal biopsies and vaginal smears were performed at the time of implantation and again during operation, in order to evaluate the effectiveness of such treatment. It was found that the vaginal mucosa became much thicker, edematous, hyperemic and more vascular, in contrast to its former atrophic and sclerotic picture. These local changes simplify the operative technic, permitting one to operate upon tissues in better conditions, possessing more elasticity and vascularization. There is one disadvantage though: increasing hyperemia leads to more intensive bleeding which, of course, requires a more careful hemostasis. Nevertheless, healing takes place under excellent conditions. Hormonal implantation has the advantage of permitting a uniform, constant and prolonged hormonal concentration in the blood.

(In these days of oral estrogenic therapy with all its convenience, satisfactoriness and flexibility, I confess that I have not been able to work up the slightest interest in the various

Cases are presented which illustrate the course of the disease, its causes and cure. Mechanical treatment proved immediately successful in all but 2 cases. In 18 cases normal menstruation was restored. There was an appreciable difference between the previous and renewed menstruation in 9 cases, in several of which the mucous membrane was examined. The characteristic microscopic picture was as follows: besides the area in which cyclical phenomena were well developed and adequate, other areas were found in which only proliferation could be recognized, while secretion was inadequate; and other areas showed scar tissue changes and closed inactive glands. In 2 cases menstruation in weaker form recommenced only after several months had passed. In one of these the amenorrhea had lasted for almost 5 years prior to treatment, and in the second case sounding was unsuccessful and led to perforation. In summary, the author states that when amenorrhea had lasted up to a year, the ratio between normal and weak menstruation was 16:5. In cases where it had continued longer the ratio was 2:5.

The writer discusses the question of how to explain the stricture in the vicinity of the inner os. In his opinion, under certain conditions, the uterus reacts to curettage by tetanic contractions which may pass or may continue so long as to become permanent. The contraction of the circular muscles around the uterine os causes the os to narrow at the close of any abrasion. In the cases under consideration here, prolonged spastic stricture becomes organic in the course of time.

The second question is: is the mechanical factor of narrowing the os sufficient to account for absence of menstruation? The reply would be affirmative if this factor were to inhibit the hormonic cycle, or if the blood were to accumulate behind the stricture. However, the hormonal cycle is not affected and ovulation remains normal. What is affected is the reaction of the uterus to hormonal stimuli. The endometrium remains in a state of entire quiescence for a long time. It is restored to activity as soon as the sound is introduced into the uterus. This would be impossible without involving the nervous system; and we must assume that both inhibiting and restorative stimuli are transferred by the reflexes to the point where their effect is exerted.

(If I interpret this paper correctly, the author is trying to establish the point that such strictures of the internal os as he describes produce not merely a retention of menstrual blood, but actually interfere with the normal cyclical hormonal response of the endometrium, thus bringing about a genuine amenorrhea rather than a mere cryptomenorrhea. Why this should be so does not appear clear. There are many much more common types of gynatresia than that involving the internal os. The two most common are probably that due to imperforate hymen and that caused by acquired and complete atresia of the external os following improper use of the cautery, conization, operation or radiotherapy. In all such cases the menstrual cycle goes on, with gradually increasing accumulation of retained menstrual blood, and with often well-defined menstrual molimina.

The author reports that only "several" of the endometria in his surprisingly large series of 29 cases of this particular disorder were examined microscopically, so that his deductions concerning the group as a whole cannot be accepted without question, and without confirmatory studies by others.

While strictures of the internal os can of course occur from such clinical causes as he enumerates, I do not believe that many clinics would consider the incidence as high as the

THE MENSTRUAL CYCLE

AMENORRHOEA TRAUMATICA (ATRETICA)

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Following complicated labor or abortion a stenosis or blockage of the internal cervical os may occur under certain conditions, thus producing amenorrhea. This amenorrhea is not functional but organic; ovulation continues but the uterus does not react and the endometrium remains in a state of inactivity. Stenosis may occur under the following conditions: (a) Curettage during the puerperium, because of a potential polyp or uterine atony. (b) Curettage for a "missed" abortion. (c) Single, or repeated, curettage after a spontaneous or induced incomplete abortion. (d) Curettage for a hydatidiform mole. (e) Severe postpartum atony without instrumental but with other mechanical interference (manual removal of placenta, intrauterine packing). The degree of resultant stenosis varies from complete occlusion to a slight narrowing.

The outstanding feature in diagnosis is the absence of menstruation, though sometimes there is slight spotting. There may be pain in the lower abdomen and back once a month, and at the same time the patient develops the usual allergic or vegetative disturbances specific to her menstruation. The basal body temperature is biphasic. Upon sounding a block is encountered at the level of the internal os. The amenorrhea may persist for months and years. Appropriate therapy brings about a return of menstruation, which is not always of the same intensity and duration as previously. In such cases, lapse of time and extent of injury are of major importance.

Treatment of amenorrhea traumatica is surgical and not hormonal. Following disinfection and bimanual examination to determine uterine position, the cervix is gripped and an attempt made to pass a sound into the uterus. If resistance is met, the attempt is repeated with narrower sounds. When one of these succeeds in passing the obstacle, the cervical canal is gradually dilated. The intervention is ended when difficulty in dilatation is met. Menstruation will ensue at the proper time, namely 4 weeks after the last menstrual pains. If the stricture is so great that even a fine sound does not pass, operation should be stopped. In most cases the slight mechanical irritation of the unsuccessful attempt will prove sufficient to initiate the onset of menstruation.

During the 3 years 1944–1946, 29 cases of traumatic amenorrhea were dealt with. The causes of amenorrhea are tabulated. Eleven patients had metrorrhagia postpartum; 7 had missed abortion; 8 had incomplete abortion; 2 procured abortion; and one had hydatidiform mole. Twenty-two patients had curettage; 5 of these had repeated curettage. There was one manual removal of the placenta and one packing of the uterus.

the roentgen rays may mechanically cause rupture of ovarian cysts which tend to inhibit proper menstruation. That roentgen therapy may act in a manner similar to surgical removal of a persistent corpus luteum is suggested. Other cases suggest action from roentgen-ray effect on the pituitary, as these cases had hypopituitary features. In certain cases the effect of roentgen therapy might be considered as one of general endocrine stimulation. There is no doubt that the younger the patient the better the result of treatment.

The technic of irradiation is described.

The author concludes that roentgen irradiation, properly administered, is harmful neither to the mother nor to the offspring and that it has proved a valuable therapeutic procedure for the treatment of amenorrhea and sterility in women.

(The author of this paper has been perhaps the most enthusiastic of the advocates of this plan of therapy, which has been commented upon in the Survey from time to time as abstracts have appeared of papers dealing with the subject. Kaplan's series is a large one and I believe that the results which he reports are better than those of most others who have employed the method. Furthermore, they are better than most of us could report from the constitutional and endocrine therapeutic plans more frequently employed by most of us. Many excellent gynecologists use roentgen therapy in cases of amenorrhea and sterility, but there are others who use it only infrequently or not at all.

Such reports as that of Kaplan do not indicate any appreciable deleterious effects upon either the patient or her offspring in the event that pregnancy supervenes, nor is there any very impressive evidence in the literature along this line. I suppose the consideration which has inhibited wider use of the plan is the fear that the harmful effects may fall, not upon the offspring, but upon the third generation. That this is a real hazard in the case of certain experimental animals appears to have been established by the work of Clarence Little and others, but whether such observations apply to the human animal we do not know, nor is there any body of evidence as yet available from clinical experience alone.

Whether, therefore, a gynecologist is to employ x-ray therapy in these cases will depend on his evaluation of the as yet very incomplete and uncrystallized evidence pro and con. As already stated, many good gynecologists use the method, though not always with the good results reported by Kaplan, and they can scarcely be criticized when one considers the very common inadequacy of endocrine therapy in many cases of amenorrhea, especially that of primary type. Since amenorrhea in itself is entirely harmless, it is the commonly associated sterility which is the real target of treatment in most cases, especially when the desire of the patient for children of her own is as desperate as it so often is.—Ed.)

TREATMENT OF THE MENOPAUSE

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The author's purpose in writing this paper is to stress the psychosomatic approach to the treatment of the menopause. In practically all of the complaints associated with the menopause the vegetative nervous system plays a major

author's, as indicated by the report of 29 cases. His hypothesis as to the explanation of such factors, attributing the chief role to prolonged tetanic contraction of the circular muscle around the internal os, appears rather far-fetched. A more logical one would seem to be that of adhesive inflammation with later cicatricial contraction.—Ed.)

THE USE OF HIGH VOLTAGE ROENTGEN THERAPY IN THE TREAT-MENT OF AMENORRHEA AND STERILITY IN WOMEN

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This study comprises a review of 338 cases of amenorrhea and sterility treated by roentgen therapy. Four of these patients did not complete the prescribed course of therapy; therefore, only 334 cases were fully treated. Of these, 33 were unmarried and 301 were married. Two hundred and seventy-four cases were followed up; 12 unmarried and 48 married cases were not traced. Of the 274 cases followed, favorable results were achieved in 12 unmarried and 198 married women; and in 9 unmarried and 55 married women treatment failed.

In the favorable result group of 198 married women, after regulation of menstruation, 90 became pregnant and went to term and delivered 101 normal children; 45 boys and 56 girls. Four women are still pregnant. Thirty-two additional cases became pregnant following treatment, of which 18 miscarried, several more than once, 2 had ectopic pregnancies, one gave birth to a stillborn child, 3 gave birth to normal children who died shortly thereafter, 6 aborted, some intentionally, there was one abnormal birth, and one case was deliberately therapeutically aborted.

Of the 301 married women treated, 34 had previous miscarriages, 16 had abortions, 7 had stillbirths, one had an ectopic pregnancy, 3 had children who died at birth, and 34 had one or more live children before irradiation.

Of those who became pregnant after treatment, 20 had more than one child after treatment.

The total number of patients who had normal full term pregnancies after treatment was 90.

Of those who responded successfully and bore children following irradiation, 6 had previously borne children and one of these also miscarried; 7 had miscarriages, 2 had stillbirths, and one had an abortion. One case which responded had miscarried before irradiation and miscarried twice following irradiation.

The author reports a number of cases which illustrate various possible effects of roentgen ray therapy. Some cases responded to roentgen therapy to the ovaries alone, and seem to bear out the assumption that these organs are stimulated by such therapy. One case suggests that the roentgen rays stimulate an underdeveloped uterus. Two other cases tend to bear out the assumption that

some menopausal women. More frequently, I believe, they are the result of fears and mis-apprehensions concerning the significance and supposed hazards of this phase—the fear of insanity, the fear of getting fat, the fear of cancer, the fear of the loss of physical and sex attractiveness to the husband, etc.

In spite of all the popular education of recent years there are still many women, some-times reasonably intelligent otherwise, who cherish such wrong ideas, leading to all sorts of functional disturbances, quite apart from the typical vasomotor symptoms which are un-questionably the result of ovarian hormone withdrawal. This latter group of symptoms is likely to be more pronounced in women who constantly worry about such things as I have mentioned above, and in turn such functional disturbances as nervousness, irritability, insomnia and digestive disturbances are likely to be most marked in the minority of women who suffer with really severe vasomotor disturbances. There is some degree of reciprocal relationship between the two groups of symptoms, and they cannot be sharply separated into those clearly due to hormone withdrawal and those due to psychogenic factors alone.

The fact remains that psychosomatic treatment, to use again a term which is rapidly becoming something of a cliché, is often far more important than hormone therapy. The latter is anything but a routine part of the management of menopausal women, only a frac-tion of whom need any at all. Education, simple instructional and reassuring talks, general constitutional measures and perhaps occasional simple nerve sedatives without any estro-genic therapy will be more helpful to more women than is estrogen therapy with complete disregard of the other measures which have been mentioned.—Ed.)

A COMPARISON OF ORAL AND VAGINAL EPITHELIAL SMEARS

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Vaginal smears have been shown to be useful in studying the menstrual cycle, and it was felt that similar changes might be reflected in the oral mucosa, since the latter possesses certain histological features in common with the vaginal mucosa. The hypothesis that stained scrapings from gingival surfaces might be useful in evaluating endogenous estrogen levels was drawn from the previous studies of Ziskin on the effects of ovarian and other hormones on the oral mucous membranes.

For the present study, oral epithelial smears consisted of scrapings taken from the surface of the cheek mucosa and from the keratinized gingivae by lightly passing a thin flat metal blade over the tissues. The vaginal smears were ob-tained as described by Papanicolaou. Oral and vaginal smears were compared in a group of 23 women. Case 1 was that of a girl with secondary amenorrhea; Case 2 was a normal pregnancy; Cases 3 to 6, inclusive, were in menstruating women with fairly normal cycles; Cases 7 to 16, inclusive, comprised 10 middle-aged women, all menopausal, presenting the complaint of oral burning or dry-ness of the mouth and throat; and Cases 17 to 23, inclusive, were 7 women of menopausal age without oral complaints, to serve as controls for the 10 cases of glossodynia.

precipitating role. It is believed that the disturbance of the vegetative nervous system and other body systems arises from a decrease in ovarian function. This produces an upset in normal function of all the other glands of internal secretion, which in turn results in increased strain on the autonomic nervous system primarily, and on all other body systems.

It may be asked why certain women have menopausal symptoms when ovarian function declines only a little, and others have no symptoms even though ovarian function ceases completely. There is evidence to support the belief that this is due to variation in the stability of their vegetative nervous system and its ability to adjust to stress and strain. In this connection it is interesting to note that women are likely to exhibit at the time of the menopause, symptoms associated with those systems which gave evidence of instability earlier in their lives.

It is the author's contention that the rise and fall of ovarian function in women is a normal physiological process, and that treatment with estrogens to unduly prolong or sustain a higher estrogen level in the blood is unnatural, artificial and at times a harmful or dangerous practice. It would seem much more logical to treat the imbalance of the oversensitive vegetative nervous system which is unable to stand the stress of the change in ovarian activity, rather than to concentrate on treating the glandular system which is behaving normally and going through its regular phase of declining activity.

There is little doubt that the psychological effect of hormone injections is often just as important as raising the blood estrogen level in controlling the symptoms of certain patients. It would seem more logical to give the woman her much needed reassurance than to resort to injections for their psychotherapeutic value. Novak states that only a minority of women require organotherapy, and Hamblen rightly comments that when psychotherapy and mild sedatives will suffice, there is no need for organotherapy.

The writer suggests that the logical treatment for the menopause should be: (1) Reassurance or psychotherapy in all cases. (2) No other treatment in very mild cases. (3) Autonomic nervous system drugs in moderate cases. (4) A combination of estrogens and vegetative nervous system drugs in severe cases, but the estrogens should not be continued longer than a few months and the other drugs should be stopped within 3 to 6 months and then used only as required. (5) Treatment of specific systems as indicated, i.e., bromides for restlessness and irritability, advice as to diet and elimination for gastro-intestinal symptoms, heat, salicylates and massage for arthritic symptoms, and so on, paying particular attention to the patient's complaints.

These patients are going through a very difficult period of adjustment and deserve our best care and understanding. It is not fair to put them off with some hormones and make no attempt to adjust their underlying difficulties with proper medicinal and psychosomatic therapy.

(The psychosomatic approach in the treatment of the menopause is important enough, but I doubt whether the "strain on the autonomic nerve system" produced by ovarian hormone withdrawal is the chief factor in the nervous and psychic symptoms exhibited by

has comparatively little practical value as regards progesterone. Body basal temperature seems to have established itself as a reasonably good indication of the approximate time of ovulation, and is of chief value in women with very irregular cycles. A number of studies have confirmed what would almost a priori seem reasonably certain, that progesterone is the hormone responsible for the slight elevation of temperature at or immediately following ovulation persisting throughout the lutein phase of the cycle, and carrying over into early pregnancy if this supervenes. The reader may be referred to 2 very recent studies which demonstrate the correctness of this view (Buxton, C. L. and W. B. Atkinson, J. Clin. Endocrinol., 8: 544, 1948, and Davis, M. E. and N. W. Fugo, Ibid, 8: 550, 1948).

Finally, because of its extreme simplicity, endometrial biopsy will continue to be the most practicable method of determining the hormonal status of the individual woman's ovaries, and the reaction of that woman's endometrium thereto. While repetition of the biopsy may be necessary in certain cyclical studies, a single biopsy, done in the premenstrual stage, often gives the requisite information from this standpoint.

One of the most frequent indications for biopsy is to determine whether or not ovulation is occurring. In spite of one or two objections to its validity, I believe that an unquestionably progestational endometrium may be considered to be pretty reliable evidence that the woman has ovulated. The preferred time for the biopsy is at or immediately after the first appearance of menstrual bleeding. This time is selected not only to avoid damaging a possibly very early implantation of a fertilized egg, but also because of the uncertainty, especially in women with notoriously irregular cycles, of selecting a phase at which the endometrium may really be expected to show good histological evidence of ovulation if this has occurred.

On the other hand, especially in the case of women living at a distance, menstrual instead of premenstrual biopsy is not feasible. In such cases one can avoid any theoretical hazard of damaging a fertilized egg, slight though this may be in women whose problem is a long-standing sterility, by simply advising the couple to abstain from coitus during the particular cycle. While I have in most cases done these biopsies within the first 12 hours of menstrual bleeding, and while these usually permit of proper histological interpretation, there are occasional exceptions in which autolysis and degeneration of the endometrium even in early stages of menstrual bleeding make histological examination definitely less satisfactory than that of the premenstrual endometrium. As a matter of fact, the examination of the latter practically always yields tissue definitely more satisfactory from a purely histological standpoint than is obtained after menstruation has begun.—Ed.)

MENOMETRORRHAGIAS OF THE CLIMACTERIUM AND THEIR TREATMENT BY RADIUM

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The author reports his experience with radium treatment in 7 cases of menometrorrhagias of the climacterium. In all cases curettage revealed cystic endometrial hyperplasia, and in 1 case there was a fibromatous uterus also. The ages of the patients varied from 30 to 73. The author considers radium a valuable therapeutic agent in selected cases of functional bleeding and of hemorrhages from myomas in the climacterium, when handled by an expert. Doses are calculated according to each case and according to the advisability of steriliz-

From these studies it was concluded that the oral smear, despite its technical advantages, cannot replace the vaginal smear as a method of determining hormone levels in women. It was found that the oral and vaginal epitheliums show parallel changes in degree of cornification during the menstrual cycle and during estrogenic treatment in deprivation states. Slight hormonal changes are more readily discernible in the vaginal smear than in the oral smear. Consequently, cyclic hormonal changes as seen in the normal menstrual cycle may be better evaluated by means of the vaginal smear. Estrogen deprivation states produce low cornification in both sets of smears, while response to estrogenic treatment is more strikingly demonstrated in the vaginal smear than in the oral smear. The vaginal smear, while not infallible, is a better indicator of ovulation time than the oral smear. 25 figures.

(Almost a priori it would seem far-fetched to think that the results of oral epithelial smears would constitute as good an index of ovarian hormone activity as the vaginal smear, in view of the fact that it is the genital mucosa which we look upon as a sort of specific end-organ of the activity of these hormones. As a matter of fact, it will no doubt surprise many to know that there are any cyclical changes at all in the oral epithelium, although one gets the impression that these were found to consist chiefly in variations in the degree of cornification. Even the vaginal smear is not a very reliable or convenient indicator of ovulation, not being comparable in this respect with the endometrial reaction as determined by endometrial biopsy.—Ed.)

THE VALUE OF THE BODY BASAL TEMPERATURE, VAGINAL SMEAR AND ENDOMETRIAL BIOPSY IN THE DIAGNOSIS OF FUNCTIONAL DISTURBANCES OF THE OVARY

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The value of these 3 semiotic procedures in the diagnosis of functional disorders of the ovary is emphasized by the authors. The latter studied normal women, women with progesterone deficiency, without ovulation and with estrogenic deficiency. In normal menstrual cycles the temperature curve proved to be of the biphasic type, the vaginal smear revealed maximum estrogenic activity and the endometrium a typical, mature progestational picture at the beginning of the menses. When there is progesterone deficiency, the basal temperature curve is flat or deficient; the vaginal smear is normal or slightly hypo-estrogenic, and the endometrium reveals a not entirely mature progestational picture. In cases of estrogenic deficiency, the basal temperature shows a monophasic type of curve, the vaginal mucosa is hypotrophic and the endometrium is either atrophic or presents minimum signs of proliferative activity.

(All 3 of the procedures discussed by the authors have their place, but all have their limitations. The vaginal smear, for example, gives one an idea of estrogenic activity, but

Such cases are clinically manifested in 3 forms: first degree amenorrhea, more or less periodic metrorrhagias simulating normal menses, and irregular metrorrhagias or metrorrhagias alternating with periods of amenorrhea. These various manifestations represent gradually increasing degrees of anovulatory cycles: short, relatively long and persistent.

Surgical treatment is advised whenever such cases do not respond to curettage or conservative measures such as organotherapy, and when they reveal under careful pelvic examination, large ovaries (Bartel Herr's white ovary or Salaber's dysplasic ovary). Histological examination of the latter reveals beneath a thickened albuginea, several small follicular cysts with granulosal cells still relatively preserved and hyperplasia of the theca interna as well as sclerosis and edema of the stroma.

The 20 cases treated by bilateral partial resection of the ovaries were grouped as follows: 12 with functional bleeding; 5 with first degree amenorrhea, and 3 with hypomenorrhea and sterility. Their ages varied from 21 to 43 years. In the first group there resulted 5 pregnancies, 5 normal cycles and 2 failures (91 per cent of success); in the second group, 4 normal cycles and 1 failure (80 per cent of success); in the third group, 3 pregnancies (100 per cent of success). Follow-up studies varied from 2 to 8 years in 17 cases; the remaining 3 were traced for 1 year only.

The author qualifies these results as excellent and strongly recommends such plan of treatment in cases of anovulatory cycles showing a tendency to recur or persist and accompanied by enlarged ovaries.

It might well be that a considerable reduction of the ovarian tissue as a result of the operation re-establishes the altered ovarian-pituitary relationship.

(The monophasic cycle spoken of by the author is obviously another term for what we commonly speak of as the anovulatory cycle, and the "severe monophasic cycle" another and not so good substitute for the common anovulatory type of functional bleeding, the kind to which Schroeder originally applied the designation of metrorrpathia hemorrhagica. I have on various previous occasions gently chided our South American colleagues for their love of eponymic designations. How many of you had ever heard of a Bartel Herr's white ovary or a Salaber's dysplasic ovary? Neither had I.

Various authors for a great many years have suggested bilateral resection of the ovaries in the treatment of this form of functional bleeding, and the fact that the method has never established a place for itself is pretty good evidence that the results have not been satisfactory. I suppose that the method has suggested itself to some clinicians on the naive assumption that if thyroid resection is beneficial in hyperthyroidism, ovarian resection should be helpful in cases which some, very incorrectly, look upon as simply hypergonadal in character. In the case of the ovary the problem is a much more complex one than in that of the thyroid.

As a matter of fact, exactly the same operation is advocated by some, especially Stein, in certain selected types of amenorrhea. I have no doubt that in some of these the results are favorable, probably because of the greater concentration of a continuing pituitary gonadotrophic effect upon a reduced ovarian surface. On the other hand, I have seen, and others have undoubtedly seen, functional bleeding of anovulatory type in patients who, for example, have previously had removal of one ovary and perhaps part of another. Simple reduction of the ovarian registering board for the pituitary gonadotrophes is certainly not the answer in the therapy of functional bleeding, the mechanism of which is still not fully understood in spite of the real advances which have been made in recent years.—Ed.)

ing the patient or not. They differ according to the age of the patient, the clinical picture, the presence of myomas, the size of the uterus, etc. For sterilizing purposes, the dosage varies around 1800 mgh, depending on the age of the patient and the size of the uterus. Radium exerts a rapid effect on the endometrium and on the ovaries; thus, its applicability in the treatment of severe functional bleeding. When applied in small doses in patients under 40, recurrences of bleeding can occur, and this may happen either with radium or with x-ray. The general menopausal symptoms do not get worse in those cases treated by radium. Libido is not altered. Neither does hypertension constitute any contraindication for radium treatment.

(What the author states as to the value of radiotherapy in the functional menometrorrhagias of the menopause can be extended also to the treatment of small or moderate sized myomas at the same age period, when these are associated with abnormal bleeding. As a matter of fact, the bleeding in these cases is often of dysfunctional nature, the myoma being only incidental. Radiotherapy, however, should never be resorted to in either of these 2 groups without preliminary curettage to eliminate malignancy. This procedure will likewise eliminate submucous growths which would lead to a preference for surgery over radiotherapy.

The dosage of the latter which the author recommends should be ample to abolish ovarian function, but it is to be remembered that marked variations exist in the degree of radiosensitivity of individual ovaries. Some are extremely radioresistant in this respect, so that ovarian function may reassert itself after a lapse of many months. This is disappointing to the patient and may be disconcerting to the doctor, as he may in some cases feel impelled to repeat the diagnostic curettage before giving further radiotherapy. On the other hand, there are some ovaries which are singularly sensitive to radiation, so that even comparatively small doses will bring about permanent abolition of ovarian function.

There are differences in opinion and practice as to the minimum age at which radiotherapeutic induction of the menopause is the method of choice over surgery in the treatment of otherwise intractable bleeding, and the individual circumstances of the case are often, as they should be, the determining factors in the case. No one would hesitate to use this method in the woman of 45 to 50 or over, but in the early 40's or late 30's, many would choose surgery, with the feeling that the ovaries are more important than the uterus in women of this age. The mental attitude of the patient, after a fair presentation of both sides of the question, is of importance in making such decisions. Such a preliminary discussion is always advisable, and may at times save the surgeon later embarrassment.—Ed.)

SURGICAL TREATMENT OF THE SEVERE MONOPHASIC CYCLE

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Obst. y Ginec. Latino-Amer., 5: 629–634, 1947

The author reports the good results achieved in the treatment of 20 cases presenting the so-called severe monophasic cycle, by performing a subtotal bilateral oophorectomy. As monophasic cycle, he means those cases presenting a proliferative or hyperplastic endometrium with complete absence of secretory activity, while the cyclic ovarian changes are just limited to the follicular stage.

The temperature elevation in such patients is apt to be most marked just before menstruation, and such a premenstrual rise is looked upon by phthisiologists as a valuable diagnostic point. Many likewise consider a postmenstrual elevation as of unfavorable prognostic significance, though this would apply chiefly to somewhat more advanced cases.

Although amenorrhea may be a very early symptom of tuberculosis, it is also often seen in the very advanced cases, as a manifestation of the general debility and the probably secondary trophic effect upong the ovary. As a matter of fact, if excessive instead of deficient or absent menstruation is observed in late stages of pulmonary tuberculosis, one should always suspect secondary tuberculosis of the genitals.

The second group of cases distinguished by the author is that in which the tuberculous involvement of the endometrium is sufficiently marked to interfere with its normal response to the ovarian hormones. It is quite certain, however, that in many of these the hormonal function of the ovaries is likewise at fault, so that the two groups cannot be quite as sharply delimited as the author implies. The fact that sterility is not infrequently a result of early tubal tuberculosis, and that in not a few of these cases endometrial biopsies have shown endometrial tuberculosis (5 per cent, according to Sharman and Schokaert) would indicate that some degree of local endometrial involvement is not incompatible with normal ovarian function. This is not surprising, since even marked degrees of nontuberculous chronic endometritis may be found in women who are menstruating with essential normality. However, in other cases of extensive and longstanding chronic endometritis, abnormalities of menstruation are seen, though more frequently in the form of menstrual excess or arrhythmia than amenorrhea. One cannot, therefore, exclude consideration of the primary ovarian factor in the evaluation of amenorrhea in the case of endometrial tuberculosis, although the vaginal smear studies of Achard indicate that in at least some cases the local factor is the important one.

The only point in Achard's paper with which I would take issue with him would be in his recommendation that progesterone instead of estrogen be employed in the treatment of tuberculous patients with amenorrhea. I do not think that any hormone therapy at all should be used. The amenorrhea is harmless and the underlying tuberculosis is the all-important disease from the patient's standpoint. It is this alone which should be treated. With arrest of the tuberculous process menstruation will re-establish itself without hormonal therapy.—Ed.)

STUDY OF AMENORRHEA IN THE TUBERCULOUS WOMAN

A. ACHARD

The amenorrhea observed in women with tuberculosis is classified under 2 groups: 1) amenorrhea with ovarian cycle only; 2) amenorrhea with no ovarian cycle. In the former, the ovarian function is normal but the endometrium does not respond to its hormonal impulses because there is a tuberculous endometritis, either transitory or definitive. In tuberculous women, the amenorrhea is mainly due to the endometrial factor, for most cases have no active pulmonary lesions or perhaps only mild ones. And these are the patients who seek medical advice complaining of sterility. In the latter group, on the contrary, the ovarian factor plays the leading role, and it is with this group that the author is especially concerned in this study. It includes those cases that are more apt to be seen in tuberculosis hospitals. The mechanism by which tuberculosis acts upon the ovaries in order to produce amenorrhea is still difficult to explain. However, since the direct lesion of the ovary by the Koch bacillus is quite rare, it seems more probable that the ovarian function is disturbed through the germ toxic activity, which inhibits the normal development and maturation of the follicles. Amenorrhea of tuberculous patients can still be divided into active and silent forms. In the former group are included those cases which present menstrual molimina at the time of the supposed menstruation; in the latter group, the cases present neither local nor general symptoms of glandular activity.

The material studied by the author comprises 50 cases of amenorrhea at the Saint Bois Hospital for tuberculous patients. In these, hormonal activity was searched for by means of the vaginal smear test and endometrial biopsy. It was found that in the group of cases of active amenorrhea, the vaginal smears revealed either acceptable or normal estrogenic activity, whereas the endometrial biopsy showed normal proliferative endometrium. On the contrary, the cases of silent amenorrhea merely revealed atrophic changes, suggesting lack of ovarian activity. These findings are of clinical and therapeutic interest. First, they suggest the inconvenience of treating tuberculous patients with the active type of amenorrhea with estrogenic hormone; and second, they indicate more rational treatment by means of progesterone instead. Patients with silent amenorrhea should not be included in this hormonal plan of treatment.

(The distinction which the author draws between his 2 groups of cases in this interesting study is a real one and not without clinical importance. In general it would appear that in the early case of tuberculosis of the genitals, in which there is likely to be little or no local involvement of the endometrium, the amenorrhea which is frequently observed is due to hormonal factors, probably the result of the toxic effects of the tubercle bacillus. It is this same type of amenorrhea which is not infrequently a symptom of even incipient pulmonary tuberculosis. I have seen a number of patients, usually quite young, whose only presenting complaint was amenorrhea, but in whom further questioning and study revealed slight evening elevation of temperature, a persistent slight cough, some loss of weight and general weakness, with definite x-ray evidence of early pulmonary tuberculosis.

GONOCOCCIC SEPTICEMIA

M. Salas Martinez

Mexico

The author reports a case of septicemia of gonococcic nature in a 13-year-old girl who finally died of the disease. The infection, probably genital in origin, presented multiple localizations. In trying to explain such a rare and unfavorable course of the disease, the author believes that the local tissue changes which occur in the genitalia during puberty, especially those of the congestive-hemorrhagic type, might have contributed to the diffusion of the disease. If this hypothesis is correct, would it not be dangerous to employ estrogens in the treatment of gonococcic vulvo-vaginitis in girls at or approaching puberty?

(Gonococcic septicemia is a rare complication either before or after the beginning of estrogenic activity. The fact that it is rare even after puberty, when cyclical estrogen production is constantly going on, would make it seem difficult to believe that estrogen therapy in the prepubertal phase would carry with it any particular hazard in this respect. If one has any lingering doubt on the point penicillin therapy would be chosen for the treatment of the vulvovaginitis, and, as a matter of fact, it appears to have superseded estrogens in the treatment of this condition in most clinics.—Ed.)

VULVA AND VAGINA

CARCINOMA OF THE CLITORIS

Aurelio Monteiro and Antonio A. Quinet
Brazil

The authors report a case of carcinoma of the clitoris in a 60-year-old woman. It concerned an epidermoid type of cancer of the second or third degree of histological malignancy and of the second degree of clinical malignancy, according to Taussig's classification, developing at the base of the clitoris, where white patches of leukoplakia were present, and therefrom invaded the glans clitoridis. An extensive vulvectomy, following Basset-Taussig's technic, was performed. The patient had an uneventful postoperative course and is at present being submitted to radiotherapy.

The authors discuss the etiopathogenesis, pathology, clinical characteristics and therapy of this condition. Even though cancer of the vulva usually develops in older women (58 years according to Taussig), the particular one developing in the clitoris is not infrequently observed in young individuals, and ordinarily gives rise to few symptoms.

Treatment ought to be surgical in those cases classified by Taussig within grades I and II, and in a few of grade III. The Basset-Taussig type of operation yields good results. Radium therapy should only be employed in the paraurethral form of cancer. Roentgen therapy ought to be limited to the inoperable cases or utilized as a complement of surgery.

(As the authors state, carcinoma of the vulva is characteristically a disease of elderly women, but there are exceptions. For example, I have recently observed an advanced vulvar carcinoma in a girl of 20. Carcinoma of the clitoris and carcinoma of Bartholin's gland are commonly included in the designation of vulvar carcinoma, although they exhibit, more especially the former, rather special histological characteristics, as well as certain special clinical properties. The surgical plan of treatment, however, is in all cases the preferred one unless there is some definite contraindication.

The radical Basset plan has apparently established itself as being the most effective, but surprisingly good results are at times seen with operations of less extensiveness, such as simple vulvectomy, or vulvectomy with superficial inguinal adenectomy. For example, I have recently seen a patient, now nearly 75, on whom I did what I thought would be a purely palliative vulvectomy 5 years ago for an extremely extensive carcinoma which had practically destroyed both labia majora. There is not the slightest sign of recurrence. Similar good results, often with very restricted operations, have been reported by Watson and his collaborators and others.—Ed.)

Among patients selected for radical hysterectomy, positive lymph node involvement is found in about half of those showing parametrial invasion. Positive lymph node involvement is found in about one-third, or less, of patients with the parametria microscopically free of cancer. It is obvious that findings at bimanual examination are not accurate for determining the probability for lymphatic dispersion. It can be assumed that a large percentage of patients have lymph node metastases when the diagnosis is established. The first nodes most frequently involved include the obturator, hypogastric, ureteral and sacral groups. More advanced involvement can extend to a second barrier in the lumbar and inguinal regions. The second group is involved only in advanced stages, and in not more than 5 or 10 per cent of patients does dispersion reach the second group without prior invasion of the first.

Berkeley and Bonney found lymph node involvement in 40 per cent of their patients treated by radical hysterectomy. The 5-year survival rate for that group was about half the rate for patients without demonstrable metastases.

The rationale of surgery is based upon the fact that cancer beginning in the cervix remains for a variable period as a process localized within the immediately adjacent tissues. Dispersions beyond margins of direct infiltration may not necessarily preclude surgical cure. Radical hysterectomy includes removal of all nodes in the primary group as well as those along the common iliac arteries in the secondary group. The parametrial tissues and vagina are excised as widely as possible. The node excision is not a block dissection, but succeeds in the removal of the accessible glands and interruption or resection of their communicating lymphatic vessels. The operation meets, therefore, the anatomical and pathological requirements for adequate treatment. It attempts also to meet surgically some of the biologic variations in tumor growth. Efficiency of the procedure depends upon the completeness of local removal and the fixed regularity at which early dispersions will follow and remain within passage ways brought into the operative field. Survival rates for radical hysterectomy show that the tumor is often confined within the volume of tissue removed. The incidence of recurrence, on the other hand, indicates the frequency with which extension or dispersion occurred outside that volume.

Between 1907 and 1936 Bonney treated surgically a total of 500 patients. During that period consultation was performed on an estimated 800 patients. There were 70 postoperative deaths, making a primary mortality of 14 per cent. The mortality was highest in the early years, and for the last 200 patients it was only 11 per cent. The operative mortality was greatest among the more advanced cases. The clinical results reported by Bonney show for the 500 patients a 5-year survival rate of 40 per cent. There were 300 patients in whom no lymphatic dispersions were demonstrable. Of that number 53 per cent were well at the end of 5 years. Definite lymph node involvement was found in 200 patients, of whom 22 per cent survived the same period.

The most recent publication by Waterman and his associates gives absolute statistics upon 579 patients treated between 1926 and 1940. In Stage I (Schmitz) the 5-year survival rate was 78.2 per cent; for Stage II it was 59.2 per

THE UTERUS

RADIATION AND SURGICAL TRENDS IN THE TREATMENT OF CANCER OF THE CERVIX UTERI

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Proponents of radical hysterectomy for cancer of the cervix are optimistic. By applying the many advances in modern surgery, they have perfected their technique and proved in well selected patients that the primary mortality need be no higher for operation than for irradiation. Selection of patients has been emphasized. It is not intended that surgery will replace established methods. In the treatment of certain selected groups, however, radical hysterectomy is presented as a challenge to irradiation. There can be no doubt that Meigs has advanced the technique of radical hysterectomy to the greatest perfection that has been attained. Upon the basis of his work there is complete justification for exploring again a procedure that once was almost entirely discarded.

Irradiation is, of course, not the complete answer to the treatment of cervical cancer. Successful treatment is not gained in all of the early lesions. To better evaluate the treatment of cervical cancer, it is necessary to consider some of the biologic properties of the disease upon an anatomical and pathological basis.

Despite origin in the same organ or type of tissue, there are wide variations in the clinical behavior of cancer in different individuals. These differences are due to variations in biologic properties responsible for infiltrating tendencies and circumstances prompting dispersion by other methods. Taylor and Nathanson have published a classic study upon methods of spread of tumors. Direct infiltration of surrounding tissues takes place along fascial planes or between laminations of tissue. In cervical cancer the paths of least resistance to invasion extend laterally into the parametrial regions along the ligament of Mackenrodt at the base of the broad ligament. Infiltrations can extend in other directions including all of the paracervical tissues. Other points of extension include the sacro-uterine ligaments and vaginal wall. Fascial planes between the cervix and the rectum and bladder inhibit direct invasion of those structures. Time required for tumor to traverse the few millimeters of distance to those organs is usually on the order of many months and sometimes years. Infiltrations extending in other directions do not meet with the same obstruction. Invasion into the parametrium also enters a zone traversed by the majority of blood vessels, lymphatics and nerves. It is by means of these structures that metastases can occur.

hysterectomy 39.3 per cent showed positive nodes. Following the use of pre-operative irradiation the incidence dropped to 11.4 per cent.

Neither Morton nor Taussig was able to demonstrate in tissues removed at iliac lymphadenectomy any constant histopathologic changes attributable to irradiation effect. The fall in incidence of positive nodes after preoperative irradiation may not represent permanent destruction of cancer. It is obvious that external irradiation alone is not apt to control tumor in lymph nodes.

The author states that there is no reason for viewing with apprehension the greater interest being manifested in surgery for the treatment of cancer of the cervix. Further exploration is justified on the basis of advance that has been made in operative procedures. The use of surgery in conjunction with radiation treatment is also important for accumulating data upon the changes produced by roentgen rays and radium on lymph node metastases. In reference to the resistance of some cervical cancers to irradiation, it is not improbable that certain infiltrating types of cancer will be found to have biologic properties for which radical hysterectomy will be a valuable adjunct in treatment.

In closing, the writer calls attention to the risks involved in both surgery and irradiation treatment, and concludes that it is the duty of those who combine radiation with surgery to produce knowledge of radiation effects on lymph node metastases, and the duty of all of those who employ radiation to seek more data upon the biologic properties of tumor growth.

(This is an authoritative and informative presentation by one who has been one of the soundest and most productive workers in this field, especially in its radiotherapeutic aspects. Especially important is the author's emphasis on the need for individualization in treatment, chiefly because of the striking individual variations in the biological behavior of cancer, entirely apart from and often quite independent of such tangible variants as histological cell gradation.

The author presents a very fair appraisal of surgery and radiation in the treatment of cervical cancer, which are to be looked upon as not purely competitive methods but rather as supplementary one to the other. Certainly no one will deny that the only rational plan in the overwhelming proportion is radiotherapy simply because surgery is justified in only early favorable cases, represented by Stage 1 and perhaps some cases of Stage 2. It is in this general group that one now encounters such variations in therapeutic thought and practice, and the simple fact is that the available statistical evidence is at present not sufficiently large or crystallizable to permit of clear conclusions.

Those who treat the surgically favorable cases radiotherapeutically can produce figures based on considerable numbers of cases with results quite comparable to those reported from clinics in which operation is preferred for the early cases. Neither school of practice can be criticized, provided always that the radiotherapy or the surgery, as the case may be, is carried out competently and adequately. This, unfortunately, is not always the case with either.

Arneson fully endorses a further exploration of the possibilities of surgery in selected cases, but this presupposes that the surgeon is fully trained in the technique of the formidable operations indicated in these cases. It will be a real contribution to demonstrate whether or not the ultimate results with such radical procedures as that of Meigs will be so clearly superior to those of radiotherapy as to fully justify the immediate hazard, which will not be as slight in all clinics as it has thus far been in a few.

The comparison which is shown in Table I between the surgical results of Bonney and those of Waterman from irradiation, showing as they do a slight superiority of the latter,

cent. These 2 groups represented one-third (34 per cent) of the total series, and together showed a survival rate of 61 per cent. For State III, the 5-year value was 28.1 per cent. Stages I, II and III comprise 76 per cent of the total series, and present a 5-year survival rate of 43 per cent. The absolute value for the total of 579 patients was 33.3 per cent. Data for comparing results between surgery and irradiation are given in Table I.

Comparison should be made also with the results reported by Meigs. Patients for surgical treatment have been selected carefully from among those with early lesions. By the end of 1945, radical hysterectomy had been done upon 91 patients without a single operative death. Thirty-six patients had been followed for a period of 3 years, with a survival rate of 77.7 per cent. Upon the basis of Bonney's work, one might expect that about 80 per cent of the recurrences to be expected would have occurred by the end of the third year. Due

TABLE I

Clinical statistics reported by Bonney and by Waterman. A comparison of surgical and irradiation results in specified percentages of total clinical material

	CLASSIFICATION	PER CENT TOTAL	FIVE YEAR SURVIVAL PER CENT
Bonney 800 patients	Operable, 500 patients	63	40
	Negative nodes, 300 patients	37	53
	Positive nodes, 200 patients	25	22
Waterman, 579 patients	Schmitz, Stages I, II, III, 442 patients	76	43
	Stages I, II, 197 patients	34	61
	Stage III, 245 patients	42	28

to Meigs' careful selection of patients, however, it is quite possible that an even greater percentage of the total recurrence rate will have developed by that time. For that reason his 5-year end results may not be particularly different from those found at the end of a 3-year period. In Waterman's report the results for 1936 to 1940 were given separately; for those years, Stages I and II represented 31 per cent of the clinical material. Among that number the 5-year survival was 71 per cent; this figure may be compared with Meigs' survival rate of 77.7 per cent. On the basis of the statistics which have been compared, there is not shown for surgery any marked superiority in clinical results.

Taussig compared results among 70 iliac lymphadenectomies with 118 Stage II (League of Nations) patients treated during the same period with radiation alone. The 5-year survival for patients with gland dissection was 38.6 per cent. For radiation alone the value was 22.9 per cent. Of considerable significance is the fact that by including more recently treated patients not then observed for 5 years, there was noted a decrease in the incidence of positive nodes. Effect of irradiation on lymph node involvement is shown also in the study made by Morton. Among his patients treated by iliac lymphadenectomy or radical

In 82.3 per cent of the cases one physician contributed to the delay; in 15.0 per cent of cases 2 physicians were involved; and in 2.6 per cent 3 physicians were dilatory. In the 113 cases showing physician delay there was a total of 136 physicians involved.

These figures demonstrate that the physician plays an active part in the problem of delay in early diagnosis. The present program has been launched for educating the physician to the opportunity afforded him to make an early diagnosis in cases of pelvic cancer.

(See comment on following abstract.—Ed.)

CARCINOMA OF THE CERVIX IN AN URBAN POPULATION

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This report concerns the treatment of cervical carcinoma in Dallas, Texas, from Jan. 1, 1936, to Jan. 1, 1946. Through various channels, data were obtained for 1,134 women who clinically had carcinoma of the cervix. The succeeding discussion is based on 992 women for whom the histologic diagnosis was available. It was impossible to present accurate statistical data; instead, only trends were determined.

One-third of the women were referred from small communities in Texas and surrounding states, while two-thirds lived in the city. The patients' ages ranged from 19 to 87 years: 5.0 per cent were under 30; 18.3 per cent were from 31–40; 29.3 per cent were from 41–50; 25.4 per cent were from 51–60; and 16.3 per cent were over 60.

Most of the women sought consultation for vaginal bleeding or leucorrhea. Where the duration of symptoms was known, the average delay from onset to time of diagnosis was 7.4 months; 6.4 wasted by the patient and one by the doctor.

Sixty of the patients had adenocarcinoma and 932 epidermoid carcinoma. The clinical grading, according to the Schmitz Classification, was as follows: Stage I, 57 patients; Stage II, 171; Stage III, 302; Stage IV, 174; and unclassified, 290.

Treatment is shown in Table V, and the 5- and 3-year survival rates for patients traced are shown in Table VI.

From this analysis, total hysterectomy followed by irradiation as contrasted to irradiation alone, did not improve the chance for a 5- and 3-year survival. Five-year survival rates for cervical stump carcinoma range from 7.6 to nearly 49 per cent. The prognosis appears to be poorer when subtotal hysterectomy is

must of course be taken with proper reservations, as I am sure the author would agree, but they, at any rate, indicate no advantage in the surgical plan.

An even greater circumspection must be exercised in utilizing for comparative study the series of cases treated with radical surgery which is being accumulated by Meigs and others. An unfortunate but inevitable by-product of the surgical revival is the fact that a certain number of surgeons are sure to undertake operation in cases not suited for this, and under the impression that they are doing radical operations to carry out very inadequate procedures. It would seem wiser for the time being to leave this important surgical experiment to clinics and surgeons especially equipped to carry it out properly.

There are of course many other aspects of the problem which are at present in a fluid and uncertain phase, such as the place of the so-called modified Wertheim operation, the most rational management of preinvasive lesions, and many others. Five or 10 years more should permit of a more intelligent appraisal than is possible now, but probably by that time other new therapeutic angles will have arisen in this field to confuse us still further.—Ed.)

PELVIC CANCER DELAY

The Organization and Observations of the Philadelphia Committee for the Study of Pelvic Cancer

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Two years ago a group of physicians in Philadelphia proposed a plan whereby they hoped to stimulate physicians to recognize their responsibility in regard to diagnostic delay in patients suffering with pelvic cancer. It was proposed to form a committee of gynecologists to study all pelvic cancer cases in Philadelphia with reference to the sequence of events occurring between the onset of the patient's symptoms, a definite diagnosis and adequate treatment, and to utilize the facts thereby obtained to inform the medical profession of their importance in diminishing the delay in diagnosis of pelvic cancer. The project was accepted and sponsored by the Philadelphia Obstetrical Society. At present, the Committee has access to all ward and outpatients with pelvic cancer in 19 different hospitals, including all the teaching hospitals in Philadelphia. The Committee meets monthly to discuss the cases in which delay is apparent. The responsible physicians are invited to attend this discussion.

Between November 1, 1945 and January 1, 1947, some 455 living patients with pelvic cancer were investigated. In 310, or 68.1 per cent, of the cases there was a lapse of one or more months from the time symptoms were first noted until a correct diagnosis was made and adequate treatment instituted. Of the 310 cases showing delay, the patient alone was responsible in 63.6 per cent; the physician alone was at fault in 24.5 per cent; and in 12.0 per cent of cases the patient and physician were equally dilatory. The combined total involving the physician was 113 cases, or 36.5 per cent.

larger average delay on the part of the doctor. An even more pointed indication for the need of both popular and professional alertness is seen in the fact that of nearly 1000 cases of cervical cancer only 57 were in clinical Stage 1, and 171 in Stage 2. The remainder were in advanced and of course clinically very unfavorable stages. Still another item chargeable to the doctor in this series was the fact that in fully ⅓ of the women, even when brought to treatment, the latter was questionable or inadequate. My own impression would be that this figure does not in any way exaggerate conditions throughout the country.—Ed.)

RECTAL HEMORRHAGE FOLLOWING IRRADIATION FOR CARCINOMA OF CERVIX

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AND

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Late intestinal complications following irradiation for pelvic malignancies are frequently encountered. By producing obliterative endarteritis and telangiectasia, the degree of damage includes all stages of tissue destruction from a simple proctitis to atrophy, stenosis, perforation or hemorrhage. Severe rectal hemorrhages which do not respond to medical treatment may require colostomy. No previous case has been reported in which intractable hemorrhage necessitated not only colostomy but also resection of the sigmoid and rectum to stop the hemorrhage.

The patient was a 47-year-old white female who complained of recurrent vaginal bleeding. She received 2400 mgm. hours of radium and 1600 roentgen units to each of four portals. Six months following this course of treatment there was a recurrence at the primary site. On this occasion she received 3600 mgm. hours from radium implants in the cervix, fundus and parametria, and 1400 roentgen units to each of four portals. Seven months after this course of treatment she was readmitted to the hospital because of rectal bleeding. The erythrocyte count dropped rapidly and so a colostomy was done. However, the bleeding continued, and after replacement of the lost blood by transfusion, the sigmoid and rectum were resected.

The distal portion of the specimen, on gross examination, showed marked induration and the mucosa had a fiery-red, finely granular appearance. There were numerous small distended blood vessels present. Microscopically, the granular portion of the distal segment exhibited a fibrous type of granulation tissue in which a small number of isolated large cells were found. These cells

done in the presence of unsuspected carcinoma of the cervix.   Where hysterectomy is indicated, a total properly done offers no greater risk to the patient than the subtotal, and does remove the possibility of later development of malignancy in the stump.

The writers conclude by stating that when it is considered that one-fifth of the women in this study received questionable or inadequate treatment, it becomes

TABLE V
Treatment

TREATMENT	PATIENTS		
	Traced	Untraced	Total
X-ray and radium...............................	432	98	530
Total hysterectomy and irradiation..............	66	23	89*
Subtotal hysterectomy and irradiation...........	80	19	99†
Other gynecologic procedure and irradiation......	8	2	10
Information incomplete..........................	180	84	264
Total...	766	226	992

* Sixty of the total hysterectomies were performed deliberately after cancer was suspected.   The other 29 were done without suspecting carcinoma or the relationship was unknown.

† Fifty-six of these operations were done one to 24 months and 41, 25 months or more, prior to diagnosis.

TABLE VI
Survival rates

CLASSIFICATION	FIVE YEAR (1936–1940)			THREE YEAR (1941–1943)		
	Total	Number living	Per cent	Total	Number living	Per cent
I............................	21	17	81	13	11	84.9
II...........................	50	32	64	55	33	60
III..........................	105	31	29.5	78	30	38.4
IV...........................	62	3	4.8	42	7	16.6
Unclassified..	91	23	25.3	61	28	45.9
Total.....................	329	106	32.2	249	109	43.9

apparent that the physician carried a responsibility for results not being better. A wider use of the diagnostic curettage and biopsy and proper visualization of the cervix would have originally given more positive diagnoses of cancer.

(The fact that the average delay in diagnosis chargeable to the patient was 6. 4 months and that for which the doctor was responsible 1 month indicates the continuing justification for the campaign of popular education now being so vigorously pushed, especially by the American Cancer Society.   It suggests also that the skirts of our own profession are not by any means clean, especially as most such statistical studies have shown a considerably

carcinoma. The former, through its hormonal activity, leads the endometrium to pathological hyperplasia. This trophomorphogenetic activity or estrogenic stimulation acting upon a postmenopausal endometrium during a long period of time may lead to the development of an adenocarcinoma.

From a clinical standpoint, it ought to be emphasized that the finding of post-menopausal hyperplasia should lead to the suspicion of a thecoma or granulosa cell tumor of the ovary, even though such tumors, when very small in size as they occasionally are, are apt to be overlooked on pelvic examination. Hence, every instance of postmenopausal endometrial hyperplasia demands a careful and close observation of the patient in order to avoid a possible carcinomatous change in such a condition.

(There is a growing number, still not very large in the aggregate, of cases of endometrial carcinoma associated with granulosal and thecal tumors of the ovary, but the authors of this paper wisely call attention to the fact that mistakes in diagnosis of the uterine adenocarcinoma can be readily made, and undoubtedly have been made in some of the reported cases. The reason for this is the fact that the postmenopausal hyperplasia so commonly evoked by these ovarian tumors may be of very atypical, pseudomalignant character, so that errors of interpretation can easily be made. This question is discussed in the paper of Novak and Rutledge, to be abstracted in a later issue of the Survey, and in that of Gusberg, abstracted in a previous issue (June).

The finding of postmenopausal hyperplasia in the absence of any palpable ovarian tumor does not justify the assumption that a small impalpable ovarian tumor of feminizing action actually is present, as was at one time accepted by many clinicians. We know that such hyperplasia may be the result of postmenopausal production of estrogen, presumably from the adrenal cortex, in the entire absence of any ovarian tumor. The authors, however, are entirely correct in warning as to the possibility of subclinical ovarian tumors under such conditions, and as to the "careful and close observation of the patient" under such conditions.—Ed.)

CERVICAL CANCER WITH METASTASIS TO BREAST

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Mammary metastasis from carcinoma of the uterine cervix is either exceedingly rare or it has been overlooked. Malignant tumors appeared independently in the breast and cervix of the same patient in several cases, but only 4 cases of primary cervical cancer associated with metastatic tumor in the breast can be found from a review of the literature.

The patient in this report was a 49-year-old white nulliparous divorcee who complained of intermenstrual spotting. She was treated with 1500 roentgen units to each of 4 portals, plus 3000 mgm. hours of radium. One year later she was readmitted because of low back pain and loss of weight. At that time a

varied in shape and size and possessed gigantic and almost black-staining nuclei. The pathological diagnosis was metastatic carcinoma, undifferentiated in the submucosa of the colon, and extensive chronic ulceration of the colon with cicatrization of the submucosa.

Two years after this operation the patient developed a mass in the region of the right colon. A resection of the ascending colon and hepatic flexure with lateral anastomosis of the cecum and transverse colon was performed. Histological studies of this tumor showed "undifferentiated carcinoma involving the large bowel." The patient made an uneventful recovery and has had no recurrence of the abdominal tumors. However, in the 7 years since her last operation she has had repeated attacks of erysipelas-like eruptions over the skin of the vulva, mons and upper thigh. It was felt that this was partially due to lymphatic blockage which favors low grade chronic inflammation.

The authors point out that the rectal damage produced by large amounts of irradiation results in a type of bleeding which is so prolonged and profuse that life is often endangered. Resection of the rectum and sigmoid may then be essential if colostomy fails to control the hemorrhage.

THECOMA OF THE OVARY AND CARCINOMA OF THE ENDOMETRIUM

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In this interesting study, the authors present 3 cases of microscopic types of thecoma of the ovary associated with what they call carcinoid or atypical hyperplasia of the endometrium. In all cases the thecoma was very small, so that it could not be felt on pelvic examination. The patients were aged 58, 51 and 69 years; 2 were already past the menopause and 1 presented hypermenorrhea followed by metrorrhagia. Atypical bleeding was also present in the 2 postmenopausal cases. Treatment consisted of total hysterectomy plus bilateral salpingo-oophorectomy and follow-up studies revealed no recurrence 3 years, 16 months and 6 months following operation.

Based upon these cases as well as other similar ones already reported in the literature, the authors discuss the possible relationship between the hormonal activity developed by the thecoma and the development of adenocarcinoma of the uterus. Up to the latter part of 1947, the literature reports an incidence of 10 per cent of such an association of lesions (98 thecomas and 11 endometrial carcinomas). They agree with Henderson, Novak, Banner and Dockerty that there is a cause and effect relationship between the coma and the endometrial

CONTRIBUTION TO THE STUDY OF ENDOMETRIOSIS

R. Cadiz Oyarzun

Mexico

During the period 1933–1942 the author was able to detect 71 cases of endometriosis, which are studied in this paper from a clinical standpoint: diagnosis, localization, types of surgical procedures performed, associated gynecological conditions, symptomatology, fertility and sterility of the patient.

The author believes endometriosis to be a disease caused by dysfunction of the ovaries with hyperestrinism. It is relatively frequent, and in the majority of cases constitutes a histological finding, though it can be clinically diagnosed when the obstetrical and gynecological past histories, and especially the menstrual history, are carefully studied. Endometriosis usually occurs between the 4th and 5th decades of life, and develops more frequently in the uterus. Of all the cases presented in this paper, only $\frac{1}{4}$ revealed this disease alone; in the remaining $\frac{3}{4}$ of the cases, other gynecological conditions, especially uterine myoma, coexisted with endometriosis. Dysmenorrhea and metrorrhagia constitute the main symptoms. As a prophylactic measure, great care should be taken on opening the uterine cavity during gynecological operations, as if a septic cavity is to be opened. Surgery is the treatment of choice, and it ought to be the most conservative possible. For those cases presenting great invasion, especially of the peritoneum, radiological castration is indicated.

(Oyarzun obviously includes in his study of endometriosis the lesion which in this country we designate as uterine adenomyosis, but which by some authors is spoken of as uterine or internal endometriosis. It is not certain that the etiology of this is the same as that of external or pelvic endometriosis, although it seems probable that a common denominator of some sort does exist. It would be foolish here to embark on any discussion of the etiology of endometriosis in general. After the more than a quarter of century which has elapsed since the first publication of Sampson on the subject, we still seem to be in the same blind cul-de-sac as far as precise knowledge is concerned.

Suffice it to say that most of us are more and more inclined to the view that the mechanism is a varied one. While I personally believe that the Meyer-Iwanoff celomic metaplasia theory is most often applicable, I also believe that the probable explanation of at least some cases is the menstrual regurgitation and peritoneal implantation factor championed by Sampson. Perhaps in a few the lymphatic transportation idea of Halban may be concerned, since genuine endometrial tissue has been demonstrated in the pelvic lymph glands in at least a small number of cases.

Finally, the small group of reported cases in which aberrant endometrium, apparently quite genuine from a histological standpoint, has been found in such locations as the arm or thigh, as in the case described by da Costa, cannot be explained by such mechanisms as those mentioned. Some suggest that the route of dissemination is by the blood stream, but it is difficult to see how the endometrial tissue passes the barrier of the lung capillaries. The other idea, also quite speculative, is that of a development from misplaced blastomeres of celomic type, with potentialities toward endometrial differentiation.—Ed.)

small nodule was found in the upper outer quadrant of the left breast. There was also enlargement of the left supraclavicular lymph nodes. X-rays of the skull showed several areas of rarefaction which were interpreted as metastases. There was no evidence of the previously existent pelvic tumor. A biopsy was taken from the node in the left breast and this was reported as "metastatic epidermoid carcinoma in the breast." The histological appearance of this tumor was identical to that of the original cervical biopsy.

DISTANT LOCATIONS OF ENDOMETRIOSIS

C. Correa da Costa

Brazil

The author reports an interesting case of endometriosis in a 43-year-old para I woman. Since the age of 25 years, the patient noticed the presence of hard, painful nodules in the inner aspect of the thighs, which used to become swollen and reddish before menstruation and finally bled at the time of the periods. These nodules, in great number, showed scarlike changes following menstruation, and new ones developed soon afterward. Six or 7 years ago similar lesions appeared in the lower mammary grooves, on both sides, in the pectoralis regions and in the neighborhood of the axillary plicae. These nodules too, became swollen and bled at the time of menstruation. Pelvic examination revealed a retroflexed uterus with a small myoma attached to its posterior wall.

A biopsy performed in one of the nodules located in the thighs revealed, on pathological examination, typical endometrial tissue (various endometrial glands, some dilated, surrounded by cytogenic tissue, and embedded in a fibromuscular matrix).

Such a rare location of endometriosis has been reported only by Navratil and Kramar and Mankin.

The author states he has seen 2 other interesting cases of external endometriosis, though in none of them could biopsy be performed. One of them was a case presenting a small nodule located on the external aspect of the right thigh; it became swollen, painful and congested before menstruation, and bled at the time of the latter. In the other case, there was a similar nodule located in the palm of one hand, which bled at the time of menstruation. The author discusses the histogenesis of these bizarre types of endometriosis based upon 2 theories: metastatic (Halban and Sampson) and embryonic rests (Robert Meyer). He accepts the latter explanation by which endometrial lesions develop from blastomeres, which have lost all potentialities except the one to give origin to endometrial tissue.

(See comment on following abstract of paper by Oyarzun.—Ed.)

THE TREATMENT OF PELVIC ENDOMETRIOSIS

H. E. Schmitz and J. E. Town

Loyola University, Mercy Hospital, Chicago, Ill.

Am. J. Obst. & Gynec. **55**: 583–590, 1948

The treatment of 130 cases of pelvic endometriosis with the aim of preserving the ovarian function and permitting childbearing is reported. The cases are divided into 4 groups according to therapy; surgery, irradiation, hormone, and untreated. There was also a group of 19 that could not be traced and therefore remained inconclusive. The average age of the cases was 32 years. Age definitely influenced the choice of therapy; the older the patient, the more radical the treatment. Some cases received several types of therapy.

The surgical group of 57 cases was by far the most satisfactory of those treated. Table 3 gives a complete analysis of this group.

Endometriosis Cases Treated By Surgery

Treatment	Complete Relief	Partial Relief	No Relief	Total	%
Radical Surgery..........	10			10	17.6
Conservative Surgery....	25	12	10	47	82.4
Secondary Surgery.......	0	1	3	4	7.0
Secondary Irradiation....	0	11	7	18	31.5
Pregnancies.............	9	2		11*	23.6

* 1 after x-ray, 1 before x-ray.

Since 7 of the patients were single the actual incidence of conception rises to 27.5%.

In the irradiation group 17 out of 29 patients were given castration doses of x-ray and gained complete relief. Twelve patients were given temporary monolysis and have remained free of discomfort. In this group 2 conceived and delivered 3 infants, an incidence of 16.6%. X-ray was also used as secondary therapy when conservative surgery failed. X-ray therapy of sufficient intensity to destroy ovarian function is indicated in cases where endometrial tissue has invaded the bowel or bladder as it obviates the necessity for surgical resection.

Androgen therapy was used in 15 cases. The diagnosis here was purely clinical; the patients were all young with minimal pathology with a definite relationship to the menstrual cycle. The author aimed at carrying these patients as long as possible without more radical treatment. Six of the group found complete relief as long as oral testosterone was administered. Eight could carry on with residual symptoms.

Twenty-five patients received no treatment. Six entered menopause; 8 with

ENDOMETRIOSIS AS A CAUSE OF OBSTRUCTION OF THE INTESTINE

P. McGUFF

Mayo Foundation, Rochester, Minnesota

An analytic study was made of 16 cases in which pathological material had been removed after a diagnosis of intestinal obstruction caused by endometriosis. Forty cases of such obstruction reported in the literature were studied also, and a series of 16 cases in all was picked for study.

The symptoms of intestinal obstruction caused by endometriosis are divided into 2 groups, one, those of extensive pelvic endometriosis, and two, those of intestinal obstruction. The most important symptom is the periodicity of all symptoms associated with the menstrual cycle and the onset of menstruation.

A clinical analysis of the data obtained from the 16 cases was made. The average age of the patients was 39 years. More than ¾ had no children. Eight complained of dysmenorrhea. All complained of abdominal pain and distention. In 4 cases, complete obstruction had developed. In 6 the obstruction was partial and in 6 there was a chronic intermittent obstruction of a low grade.

Important points in the diagnosis of endometriosis as a cause of abdominal obstruction are: acquired dysmenorrhea, sterility, periodicity of symptoms, rectal pain, uterine fibroids, and a history of progressive obstruction. If the obstruction is ileal, vomiting is present; if it is colonic, obstipation is present. The finding of a firm tumor in the rectovaginal septum is suggestive of the condition. Sigmoidoscopic examination and roentgenograms are helpful.

The treatment is surgical, usually consisting of a panhysterectomy with or without colostomy. In a young woman with normal pelvic organs, conservative operation is done on the ovaries and radical operation is done on the bowel.

Pathological analysis of the 16 cases revealed that ileal obstruction was due to kinking, while obstruction in the sigmoid and lower part was due to impingement into the lumen. Microscopically, endometrial glands and stroma were found in all layers of the intestinal wall. It is well to remember that endometriosis invades the bowel from the serosa inwardly while carcinoma invades from the mucosa outward.

A plea is made for biopsy in confirmation of the clinical diagnosis. Prognosis for the patient following an operation is excellent.

(See comment on following abstract of paper by Schmitz and Town.—Ed.)

the time of delivery. The authors believe this to be the first reported case following a normal spontaneous delivery.

The patient was a 23-year-old negro female, para i, gravida ii, who was admitted with the complaint of painful swelling of an old episiotomy scar which recurred monthly coincident with the onset of her period. Four years previously she had had a normal spontaneous delivery and a left mediolateral episiotomy was performed. It was repaired in layers using interrupted black silk sutures for the skin. Examination revealed a hard mass which was palpated the whole length of the scar.

The entire mass and scar were excised. Grossly, many blue pinpoint nodules were seen. Microscopic examination of this tissue showed endometrial glands and stroma. The patient was completely relieved of symptoms following the operation.

CHORIONCARCINOMA

P. PERNWORTH

St. Elizabeth's Hospital, Granite City, Ill.

Chorioncarcinoma in the female may follow abortion, more rarely a full term pregnancy, and is seen in $\frac{1}{3}$ of patients with a hydatidiform mole. Marchand established the currently accepted view that the tumor, like hydatidiform mole, is of fetal origin arising from chorionic villi. Clinically, the pregnancy tests depending on the presence of ovarian-stimulating pituitary hormones, are positive in all cases of chorionepithelioma.

In diagnosis, eliciting a history of past pregnancy is important. Earlier expulsion of a mole is very significant. Repeated uterine hemorrhage with a positive Aschheim-Zondek reaction suggests the presence of chorionepithelioma.

Chorioncarcinoma is among the most malignant of tumors. When the lesions are confined to excisable areas, hysterectomy is the treatment of choice. When there are generalized metastases or parametrial infiltration, surgery is useless. Radiation therapy may be instituted but the prognosis is uniformly hopeless.

The author presents the case of a patient presenting the chief complaint of continuous vaginal bleeding of 14 months' duration, since a normal delivery. Physical examination disclosed a thin, pale female with marked air hunger. There was a steady sanguineous oozing from the cervix. The uterus was hypertrophied and there was some suggestion of bilateral ovarian enlargement.

A gentle curettage revealed tissue suggestive of chorioncarcinoma. The Friedman test was strongly positive.

Following blood transfusion the abdomen was opened. The uterus appeared grossly normal. It was removed almost entirely, leaving only a narrow rim of

minimal discomfort and an average age of 30 were carefully watched; 11 refused treatment.

The authors feel that pelvic endometriosis occurs most frequently in the child-bearing age and is a major cause of sterility. Conservative treatment which will increase the possibility of conception is therefore the most desirable form of therapy.   6 tables

(Opinion is now pretty well crystallized to the effect that a good many cases of endometriosis need no treatment, and that when treatment is indicated, as it frequently is, it should be preferably surgical and preferably conservative in the case of women in whom later childbearing is important, in spite of its definitely limited possibility. The paper by Schmitz and Town presents the results in a considerable group of patients treated along these conservative lines, and the results reported justify this conservatism. Androgen therapy, it seems to me, has only a limited symptomatic application, its chief value being probably in the amelioration of pain due to residual endometriosis in patients in whom x-ray castration is undesirable. Even in these, or in the milder forms of endometriosis, I question whether simple analgesics are not just as effective and probably to be preferred.

Schmitz and Town recommend x-ray therapy in those cases in which the bowel is invaded by the endometriosis, the group which is more fully discussed in the paper of McGuff. However, the difficulty is that preoperative diagnosis of bowel involvement is often impossible. In the presence of extensive and obvious pelvic endometriosis, one can feel that obstructive bowel symptoms are almost surely due to the endometriosis, and the diagnosis can sometimes be definitely established by palpation, sigmoidoscopy, x-ray study and biopsy.

On the other hand, intestinal endometriosis is sometimes found with very little or even no such lesion of the pelvic organs, and its symptoms, especially when the ileum is the part involved, may simulate malignancy perfectly. Since malignancy of the small intestine is far more common than endometriosis, this is the diagnosis which will probably be made and surgery will be done. When the bowel mucosa is smooth and intact one can exclude carcinoma no matter how thickened and indurated the bowel wall. But this point is of more interest to the pathologist than to the surgeon, who does not get a chance to examine the interior of the excised section of bowel until after the resection has been done.—Ed.)

ENDOMETRIOSIS OF EPISIOTOMY SCAR

H. E. Schmitz

Chicago, Ill.

AND

P. Grossbard

Passaic, N. J.

Cook County Hospital

The sites at which endometrial implants occur are numerous; however, endometriosis in the perineum is extremely unusual. Reports of previous cases would indicate that it occurs primarily following operative procedures done at

but in which the degree of trophoblastic overgrowth may be so marked, and sometimes associated with at least a suspicious degree of individual cell change, that one may be uncertain as to their malignancy or nonmalignancy. Pathologists will often disagree in their interpretation of this group, although fortunately it is numerically not a large one.

The first of these 2 intermediate groups is clinically, the second histologically, of borderline type. As regards the histologically doubtful variety, the problem is similar to that encountered in other fields of pathology, notably in the now much discussed one of precursory and preinvasive cervical carcinoma.

As to the significance of the multiple lutein cysts which may be found with either perfectly benign or definitely malignant choriomas, the author appears to me to take an extreme and incorrect view. These cysts represent only a pathologic physiologic response of granulosal or thecal cells to the excessive chorionic gonadotrophic hormone produced by the excessive trophoblast characterizing either benign or malignant lesions.

The chronologic relation between a hydatidiform mole and lutein ovarian cysts is very variable. Cases have been reported in which large cysts have appeared immediately after the evacuation of a mole, but with later spontaneous regression. Again, with either hydatidiform mole or chorionepithelioma no gross enlargement of the ovaries may be palpable, although microscopically one can always expect to find some degree of the so-called hyperreactio luteinalis. Zuckerman's admonition that persistence of the cysts after evacuation of a mole should indicate hysterectomy seems unjustified, and would lead to unnecessarily radical treatment for certain perfectly benign moles.

The production of these multiple lutein cysts by hydatidiform mole or chorionepithelioma involves an interesting problem of endocrine mechanism. As already mentioned, the underlying factor is considered to be an excess of the chorionic gonadotrophic hormone. And yet, in the nonpregnant woman, the injection of even huge amounts of this hormone produces no such ovarian changes. The only explanation which suggests itself is that in the pregnant woman the chorionic hormone excess sets up some sort of augmentation or activation of the woman's pituitary gonadotrophes. As a matter of fact, Evans and his coworkers have produced good experimental evidence for such an augmentation mechanism. That this is involved with the choriomas is further suggested by the fact the lutein response in the ovaries is quite similar to that produced in animals by the pituitary sex hormones, rather than that brought about by the chorionic gonadotrophes.—Ed.)

POSTMENOPAUSAL BLEEDING FROM FIBROIDS

Lois A. Day and J. H. Pratt

Mayo Clinic, Rochester, Minnesota

Staff Meet. Mayo Clin., 23: 162–166, 1948

While uterine fibroids are responsible for abnormal bleeding in a much higher percentage of cases in the reproductive years, they do, in a small percentage of women, cause postmenopausal bleeding. Two such cases are presented in this report.

The first patient, aged 77 years, para 4, complained of an increase in the amount of vaginal bleeding that had been present since the age of 50. At the latter age, because of irregular bleeding, cervical amputation had been done, after which the bleeding lessened but never ceased occurring. It had increased

cervical tissue.   Both ovaries were subtotally resected, allowing only grossly normal strips of tissue to remain on each side.

Sections of the specimen showed syncytial and Langhans' cells which had invaded the uterine musculature.   This, together with the ovarian cysts, suggested a true malignancy rather than a burrowing mole.

Three years after operation the patient is in excellent health, and 2 interim pregnancy tests were negative.

(See comment on following abstract.—Ed.)

PENETRATING MOLE AND LUTEIN CYSTS

C. ZUCKERMANN

Mexico

Rev. Mexicana de Cir., Ginec. y Cancer, No. 10, p. 375, October, 1947

Placentomas are classified in 4 different varieties: (1) simple placentoma or hydatidiform mole; (2) penetrating placentoma or invasive mole; (3) destructive placentoma; (4) placentoblastoma or chorionepithelioma.   According to the author, the persistence of lutein cysts following elimination of a mole calls for hysterectomy in order to prevent the malignant degeneration of the tumor. A case is reported of a woman presenting amenorrhea for 3 months, hypogastric pain, slight elevation of the temperature, bloody discharge, enlarged uterus and the pouch of Douglas filled with a somewhat softened mass.   A clinical diagnosis of ruptured ectopic pregnancy was established.   Preceding laparotomy, cervical dilatation was performed in order to examine the uterine cavity; and at this time, characteristic mole vesicles were encountered.   During operation, serous fluid was found in the peritoneal cavity, whereas the uterus corresponded to a 3 months pregnancy in size and both ovaries revealed lutein cysts.   Subtotal hysterectomy and appendectomy were performed and the patient had an uneventful recovery.   Pathological report revealed a "penetrating and destructive mole" with destruction of the uterine wall in some areas.

(The division of placentomas or choriomas into the 4 groups mentioned by the author may or may not appeal to the reader as having advantages over the usual division into 3 groups.   Between the frankly benign hydatidiform mole and the frankly malignant chorionepithelioma there is unquestionably a group which is borderline either clinically or histologically, or both.   In this group must be placed certain hydatidiform moles which, so far as my own observation goes, are not histologically distinguishable from others which clinically are very benign, and yet which exhibit an inordinate degree of the intravascular penetration which to some extent is characteristic of all trophoblast, even that of normal pregnancy.   Such moles can penetrate through the uterine wall and sometimes cause serious or fatal intraabdominal hemorrhage, so that they are to all intents and purposes clinically malignant.

There is another intermediate variety which may show no undue vascular invasiveness,

but in which the degree of trophoblastic overgrowth may be so marked, and sometimes associated with at least a suspicious degree of individual cell change, that one may be uncertain as to their malignancy or nonmalignancy. Pathologists will often disagree in their interpretation of this group, although fortunately it is numerically not a large one.

The first of these 2 intermediate groups is clinically, the second histologically, of borderline type. As regards the histologically doubtful variety, the problem is similar to that encountered in other fields of pathology, notably in the now much discussed one of precursory and preinvasive cervical carcinoma.

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in the year prior to admission. Examination disclosed the corpus to be about twice normal size and movable. A small nodule was felt on its posterior surface.

The second patient, a 61 year old para 1, complained of vaginal bleeding and distress in the left lower quadrant of 3 weeks' duration. At the age of 58 she started to bleed vaginally and was given some kind of injections and vaginal treatment, after which the bleeding stopped. The authors assume that she was given radium. Examination revealed an unusually soft cervix; the corpus was about twice normal in size and somewhat fixed.

Dr. Pratt discusses the increasing difficulty in diagnosing postmenopausal bleeding because of the increasing number of women given estrogens. Fibroids as a cause of postmenopausal bleeding, although uncommon, are by no means rare, Cheek and Davis reporting 18 in a series of 514 cases and Geiger 13 in 395 cases. When the fibroids are of considerable size, hysterectomy is indicated. Radium is unsatisfactory because chronic discharge or infection in the degenerating fibroid is likely to result and because the action of radium in bleeding patients is chiefly that of destruction of ovarian function; this, or course, does not help the postmenopausal patient. Small fibroids, if removable by torsion or curettage, should be so treated. However, when carcinoma has been excluded, small fibroids can well be treated conservatively by dilatation and curettage alone if they are not fairly easily excised. The 2 patients reported herein had submucous fibroids.

In the first patient, aged 77 years, 2 fibroids were removed with difficulty through the cervix, but in the process the continuity of the posterior uterine wall was disturbed. Vaginal hysterectomy was carried out, tubes and ovaries were preserved, and the patient recovered.

In the second patient, 61 years old, the cervix was divided and a fibroid 2 inches in diameter was delivered. This patient also recovered. 1 figure.

THE ADNEXA

DIAGNOSIS AND TREATMENT OF SALPINGITIS

S. G. CLAYTON

Practitioner, 160: 248–251, 1948

The author states that the primary causes of salpingitis are: (1) gonorrhea (40 per cent of cases); (2) infection following abortion or delivery (50 per cent); (3) tuberculosis (5 per cent); and (4) infection from adjacent organs such as the appendix (5 per cent).

In gonococcal salpingitis, acute bilateral abdominal pain occurs and there is fever of 102 to 103 degrees F. (which is a cardinal point in differentiation from ectopic pregnancy). The lower abdomen is slightly distended, tender and guarded. Cervicitis and urethritis may be found. Movement of the cervix or pressure in the fornices causes pain. A well-defined mass is not felt unless a pelvic abscess or a pyosalpinx forms, which takes some days. Treatment of the primary attack is conservative, consisting of absolute rest, large fluid intake, and the injection of 20,000 units of penicillin 3-hourly, to a total of about 300,000 units. All local interference is strictly avoided. A few cases develop a pelvic abscess, which is drained by posterior colpotomy. Pyosalpinx is a rare sequel of a single attack.

In cases of salpingitis following delivery or abortion, the disease is part of a widespread pelvic cellulitis and peritonitis, and is often revealed after 3 or more weeks when the widespread infection recedes. Most puerperal cases are due to streptococci which are sensitive to penicillin, and the initial treatment is the same as for gonococcal salpingitis, although more care is needed to treat anemia and sustain the general condition.

Recurrent attacks of salpingitis are usually due to reinfection. There is pain and fever, and tubo-ovarian masses are found behind the uterus. Irregular and excessive menstruation often occurs.

The diagnosis of chronic salpingitis can be difficult. Endometriosis gives a similar clinical picture, with pain, sterility, menorrhagia and pelvic masses, although in endometriosis there is no history or evidence of infection. The indications for surgical treatment of chronic salpingitis cannot be rigidly defined. Every effort is made to conserve or restore function in a young nullipara, but once function is irretrievably lost, radical treatment is preferable to prolonged ill health. Conservative treatment consists of rest, penicillin in exacerbations, and local heat. Indications for surgery may be summarized as follows:

(1) For cases with recurrent attacks, or when conservative treatment fails to relieve pain.

(2) For cases with large masses, as they seldom respond to conservative therapy, and because the diagnosis may be in doubt.

(3) For cases with menorrhagia.

(4) For selected cases of sterility.

If bilateral salpingectomy is necessary, then total hysterectomy is often wise.

If a nullipara without history or evidence of cervicitis has salpingitis, tuberculosis should be considered, especially if the disease is insidious in onset with loss of weight and slight pyrexia. Menorrhagia is common, but amenorrhea occurs in advanced cases. Tuberculous ascites or plastic peritonitis or pyosalpinges may be found. Active pulmonary disease is present in 20 per cent of cases. Opinions differ as to treatment. If there is active pulmonary disease sanatorium treatment is advised; and radical surgery is unwise if there is widespread tuberculous peritonitis. If the disease is strictly localized in the pelvic organs, bilateral salpingo-oophorectomy gives excellent results.

(This is an eminently satisfactory review of the subject, expressing views which will be endorsed by almost all of us. The incidence of operations for salpingitis has dropped tremendously in all clinics, and this is not altogether due to the advent of antibiotics and chemotherapy, important as these have been. But for a good many years before their introduction our attitude had become much more conservative. Every gynecologist sees numerous patients in whom the tubes and ovaries are fixed and adherent, and in whom he can be quite sure that there is a chronic salpingitis, but who suffer little or no discomfort. There is no indication for surgery in such cases. On the other hand there is still a residue of cases in which the sequelae or complications of infectious storms which have swept over the tube, rather than any existing infection, may produce symptoms so troublesome as to call for surgery, and the chief indications for this are the ones noted by the author. (See also comment on following abstract.—Ed.)

SOME ASPECTS OF GONORRHEA IN THE FEMALE

C. S. NICOL

St. Bartholomew's Hospital, White Chapel Clinic, London, England

Since the advent of chemotherapy there has been a widespread belief that the problem of the control of gonorrhea has ceased to exist. This is, of course, not the case and it is in the diagnosis and contact tracing that the greatest efforts must be made to suppress gonorrhea.

An analysis of 229 patients with acute gonorrhea was made. Of this group 159 were married and 70 were single. The majority were under 30.

Contact tracing was carried out through the clinic's social service department. Efforts to trace contacts or husbands were unsuccessful in only 57 cases. The data gathered from contact tracing and from patients attending the clinic with a contact slip are presented in Tables 1 and 2.

One hundred forty patients attended on the advice of the male consort who had active gonorrhea. An analysis of the most usual symptoms, vaginal dis-

charge, dysuria, abdominal pain and arthritis, is made for patients both with and without trichomonas vaginalis infection. In 106 cases there were no significant symptoms suggesting gonorrhea. It was also found that the signs of the disease are often minimal even though the patient remains infectious.

For these reasons the author believes that it is vital to use every means available in the diagnosis of an infection. Both smear and culture were used in this study and some diagnoses were made by smear or culture alone. Positive cases were also obtained by the use of the vaginal plate technique. A discussion of a positive gonorrhea complement fixation test without a positive smear or culture result is presented. Trichomonas infection was found in 102 of the cases by tests made on first admission. In 49 cases it was demonstrated only after the administration of penicillin for gonorrhea. In 18 of the patients monilial vaginitis was found.

Seventy-four patients were examined for gonorrhea proctitis and 26 cases had positive findings. Of this group only 8 would admit any symptoms. The author feels that the examination of the anal canal and lower rectum and the taking of rectal smears should be a routine part of the diagnostic procedure in the examination for gonorrhea, since in this study 5 of 26 cases depended on the rectal findings for diagnosis.

A routine treatment of 30,000 units of sodium penicillin at 2-hour intervals was given the majority of the patients. The author feels that it is difficult to give a correct interpretation of the treatment results andhe also wishes to stress the fact that the cultural diagnosis is never a simple matter. The possibility of variation in the penicillin could interfere with treatment results also. Gonorrhea appearing after treatment may be due to reinfection. All of these variations can be found in the treatment of gonorrhea proctitis as well. 12 tables, 6 figures.

(Nicol properly emphasizes that the control of gonorrhea must also envisage a campaign of control through contact tracing, although the social service facilities of most clinics are inadequate for this purpose, and in many they are non-existent. Even municipal, state and Federal departments of public health have not as yet made impressive advances along this line. Nicol evidently believes, with most others, that cultures are much more reliable in diagnosis than smears or the complement-fixation test.—Ed.)

NODULAR TUBES

PACHECO ULLOA, M.
Chile

Bol. de la Soc. Chilena de Obst. y Ginec., **12:** 227, 1947

The author presents a detailed clinical and pathological study of 15 cases of nodular tubes. The majority of these nodules were localized in the isthmic

(66.6 per cent) and interstitial (33.3 per cent) portions of the tube. As to the etiology of such lesions, the following causes were encountered: diverticulosis due to endometriosis in 33.3 per cent of the cases; tuberculosis in 33.3 per cent; nonspecific chronic salpingitis in 13.2 per cent.

When endometriosis is the underlying cause of the nodules, the surgeon ought to bear in mind the problem of sterility. In such circumstances, a conservative operative procedure should be resorted to, consisting of the resection of the pathological portion of the tube followed by tubo-uterine implantation, even though the tube might be shown to be patent by means of insufflation, hystero-salpingography, etc. On the other hand, in women in whom the possibility of reproduction can be eliminated as a result of the age of the patient or co-existing lesions (myoma), resection of the tube constitutes the proper treatment. In cases of tuberculous tubes, the latter ought to be entirely removed once diagnosis is established, despite the age of the patient. Subtotal hysterectomy is usually performed at the same time. Salpingectomy, simple or combined with hysterectomy, is the treatment of choice for chronic non-specific salpingitis.

(The "nodular tubes" which the author discusses obviously refers chiefly to the lesion commonly spoken of as salpingitis isthmica nodosa, for the Latin designation appears to be the one most frequently employed in everyday parlance. However, Ulloa includes in his study nodular tubes produced by endometriosis, and finds this lesion present in the surprising proportion of one-third the cases, a figure certainly far higher than would be found in our own and probably most other laboratories. The disparity is no doubt to be explained by differences in microscopic interpretation. Endometriosis of the cornual portion of the tubes is of course seen, especially but not necessarily always in association with uterine adenomyosis. To justify the diagnosis the epithelium of the islets in the tubal wall must be endometrial and not tubal, and the glands should show a surrounding mantle of the characteristic endometrial stroma, with little or no inflammatory infiltration.

Salpingitis isthmica nodosa, on the other hand, is characterized by an apparent splitting up of the lumen into many small canals of various sizes. This appearance is the result of the marked proliferation and the invaginating tendency of the tubal mucosa under the influence of chronic inflammation, so that one sees many gland-like lumina scattered throughout the muscularis. In the larger of these the tubal characters of the epithelium are likely to be retained, while in the smaller ones the lining cells may be cuboidal. No endometrial stroma surrounds the canals, but almost always one finds considerable round cell infiltration.

While the lesion was by Chioriak and other early pathologists looked upon as a frequent residuum of tubal tuberculosis, and while this is certainly not a rare association, I believe that most of us find it much more frequently in non-tuberculous, especially gonorrheal, infection of the tube, contrary to the findings of Ulloa. On the other hand, the suggestions which he makes as to the treatment of this type of salpingitis under different conditions seem to be sound.—Ed.)

HEMOPERITONEUM DUE TO BLEEDING FOLLICLE. CHRONIC TORSION OF A CYSTADENOMA OF THE OVARY

D. BASSAN AND A. BODEN

Rosario, Argentina

Obst. y Ginec. Latino-Amer., 5: 667–669, 1947

A case is reported of a 16-year-old girl, single, complaining of pain in the right lower quadrant of the abdomen for the past 4 years, accompanied by nausea. Menarche at the age of 11 years. Sixteen days after her L.M.P. the pain became more severe and the general symptoms worse. Pelvic examination was omitted, as the patient was a virgin. Rectal examination was not done. Operated upon under the impression of appendicitis, there were encountered about 250 cc. of blood, with a few clots, in the peritoneal cavity. The right ovary was found to be cystic, the size of a pigeon egg, twisted, presenting in its normal portion a bleeding follicle. The latter, as well as the cystic area, was resected, followed by extirpation of a grossly normal appendix. Pathological examination revealed a ruptured mature follicle with intense congestion of the medullary portion of the ovary. No mention is made as to the nature of the cystadenoma.

As the authors state, only the pathological examination is able to distinguish a follicular hemorrhage from a luteinic bleeding. The latter, however, is generally more profuse, symptomatic and usually presents itself in the premenstrual phase of the cycle. On the other hand, follicular hemorrhage is of less amount, its symptoms are not so striking, and it appears at the supposed period of ovulation. According to Harris and Groper, 75 per cent of the cases concern bleeding from the corpus luteum, whereas the remaining 25 per cent consist of follicular hemorrhage.

Surgical treatment of both these conditions ought to be along conservative lines, especially in young women.

(Intraabdominal hemorrhage of ovarian origin may have its source in either the follicle or the corpus luteum. Often it is slight in amount, and cases of this sort may be characterized by moderate or severe pain, not infrequently at about the mid-interval, so that they probably often parade clinically as mittelschmerz. If right-sided they may easily be mistaken for appendicitis. In some instances, however, the intraabdominal bleeding may be massive, so that they are likely to be mistaken for ruptured tubal pregnancy. In the authors' case the associated torsion of the pedicle was apparently very incomplete and of short duration, since the ovary was merely resected and not removed.—Ed.)

MALIGNANT TUMORS OF THE OVARY

J. B. Montgomery

Jefferson Medical College Hospital, Philadelphia, Pa.

A review of all of the cases of malignant disease of the ovary treated at Jefferson Hospital between October, 1921 and October, 1946 is presented.

Eighty-four of the 107 patients had adenocarcinoma. Fifty-seven of this group were between 40 and 60 years. Twenty-three had a previous operation involving either the pelvic or abdominal region. The chief symptoms were pain and abdominal enlargement. Nausea, vomiting, loss of weight and backache were also noted. The average duration of symptoms was from 6 to 12 months.

Surgery was performed wherever possible and the primary tumor was removed. Unilateral oöphorectomy was done in 17 patients and of 8 with a remaining healthy ovary, 6 are living and free of disease.

The cases were studied in the light of 4 factors governing the end results of carcinoma; extent of growth, grade of malignancy, the histologic type of the tumor, and the influence of x-ray. Interpretation and interrelation of these factors are shown by the use of tables. The tumors were classified as either serous or pseudomucinous. Cystic, partly solid, and solid were classifications based on the tumor structure.

The cases were divided into the 3 grades of malignancy used by Taylor. A complete summary of the end result of each grade is given in tables 1, 2, and 3.

Sixty-eight of these graded patients were eligible for a 5-year study. Table 4 shows the results of this study.

TABLE 4

Results in Relation to Grade of Malignancy in 68 Cases Eligible for 5 Year Study.

Malignancy	Total Cases		Free of Disease Five Years	
	Number	%	Number	%
Grade 1.....................	16	23.5	10	62.5
Grade 2.....................	19	27.9	3	15.8
Grade 3.....................	33	48.5	1	3.0
Grades 2 and 3.............	52	73.5	4	7.7

These figures emphasize the influence of grading on the prognosis of ovarian cancer. The author believes that separation into grades 2 and 3 is of prognostic value, as well as the recognition of grade 1.

The gross extent of the disease is, of course, the most important factor in prognosis. In this study the cases are divided into 3 groups according to their operability. The tumor was completely operable in 19 cases, 10 of which were free of disease 5 to 24 years later. Thirty of the cases were incompletely operable and only 4 of these were free of disease for 5 years. Thirty-five were inoperable and only 1 is alive after 12 years.

Of the patients with adenocarcinoma 58 had serous papillary adenocarcinoma of whom 9 lived for 5 years. Ten had pseudomucinous tumors of whom 5 or 50% have survived. Twelve of 16 with papillary cysts are still living; only 4 of 37 with partly solid tumors survived and all 18 with solid carcinoma are dead. There were 10 cases of granulosa cell tumors; 3 are dead, 4 living for 5 years, and 3 untraced. Of 7 cases of ovarian carcinoma associated with adenocarcinoma of the endometrium only 1 is living and free of disease. Other types of tumor in the group were; 2 of dysgerminoma, both living and well, 1 Brenner tumor, still well when last examined, and one Krukenberg tumor, the patient dying shortly after operation.

Prior to 1927 massive doses of x-ray were used, given at right angles to pelvic ports. After 1927 the saturation method was used. X-ray therapy was studied in relation to the grade of malignancy and it was noted that 8 of 11 survivors with grade 1 malignancy had x-ray therapy. In grade 2, 2 survivors had incompletely operable tumors and benefited from x-ray. The value of x-ray therapy in relation to the extent of the disease is shown best in those tumors which were inoperable or incompletely so. It seemed that x-ray prolonged life in these cases. However, factors, such as the grade of malignancy, extent of growth and type of tumor, make the value of x-ray uncertain.

The author concludes that operability and malignancy are the greatest factors in determining survival. The papillary cysts are the most favorable type. He acknowledges the part played by the difficulty in getting an early diagnosis of ovarian carcinoma and suggests routine pelvic examination every 6 months as an aid in this matter. When enlargement of the ovary persists or increases especially in menopausal women, an exploratory incision should be made at once rather than waiting. 9 tables.

(Every statistical study of any large number of ovarian cancers which has ever been published has been more or less depressing, emphasizing the generally poor prognosis and the insidiousness of this form of cancer. Montgomery lists pain and abdominal enlargement as the chief symptoms, but both of these are indicative of late stages, while there are usually no symptoms of the earlier stages except in the relatively small group of functioning tumors, most often of granulosa cell type. While with cervical or corporeal carcinoma the intelligent woman may in many cases be given the alert by abnormal bleeding of one type or another, no such warning is vouchsafed the victim of ovarian cancer. All too often her first suspicion of something wrong may be the appearance of a lower abdominal mass, and not infrequently patients present themselves because of abdominal enlargement due to ascites.

Important as periodic examination is in the recognition of all forms of cancer, in none is its importance more signal than in the field of ovarian cancer. Indeed, I know of no other way for the woman to protect herself in this respect. The gynecologist is fully justified in being considerably more hardboiled in his attitude toward symptomless ovarian tumors than, for example, toward uterine myomas. The latter only infrequently undergo malignant change, but the former have much more wicked potentialities in this respect. This is not, of course, to say that every slightly or moderately enlarged ovary should be removed, for a large proportion of such enlargements are of functional cystic nature and regress spontaneously. But a cystic tumor that steadily grows beyond a moderate size, and any tumor which by its feel seems clearly solid, calls for removal.

Montgomery's results compare favorably with those of others, and appear to have been more definitely influenced by the histological grade than have been those reported by most

other authors, since the surprising proportion of 62.5 per cent of Group I survived the 5-year period.   In spite of this there is no question that the clinical stage of the disease is more important in prognosis than the histological grade, as is true of cervical cancer.

That 3 of 7 traced cases of granulosa cell carcinoma died confirms at least my own growing conviction that this type of ovarian cancer has been treated too lightly by many authors, and that it is always to be looked upon as potentially and often as very actually malignant, in spite of the fact that the degree of malignancy is of course less than that of ordinary types of ovarian cancer.   The one Brenner tumor mentioned does not belong in a paper on malignant tumors, for it is a benign neoplasm.

A large proportion of Montgomery's tumors were of papillary type, and I mention this simply to call attention to the not infrequent difficulty of histological differentiation between the benign and the malignant, a factor in statistics which is difficult to overcome, but which obviously may vitiate reports of final results.

Finally, like most gynecologists, Montgomery employs postoperative roentgen therapy, and believes it has a definitely retarding effect.   The vagaries of these tumors make it almost impossible to study the effects of such therapy in any scientifically controlled fashion.   While most of us employ it, I suspect that many do so rather unenthusiastically, and with the feeling that it is about the only additional procedure which can be employed to give the patient a chance for recovery, or, far more often, for prolongation of life and amelioration of symptoms.—Ed.)

MALIGNANT GRANULOSA—CELL TUMOR IN AN INTRAPLENIC OVARIAN GRAFT IN A CASTRATED MALE MOUSE

M. H. LI

Yale School of Medicine, New Haven, Conn.

Granulosa cell tumors and luteomas have been developed in intraplenic ovarian grafts in castrated male and female mice.   This is a report of metastasis and successful transplantation of such a granulosa cell tumor.

Male and female mice of several different strains and hybrids were used.   They were castrated and received an autoplastic or homoplastic ovarian graft in the spleen.   Some were given weekly injections of 16 micrograms alpha-estradiol benzoate, 1.25 mg. testosterone propionate or 1 mg. progesterone.   Unilaterally gonadectomized mice with intraplenic grafts were used as controls.   The experiment lasted 10 months.

There was apparently no strain limitation in the development of the tumors. Tumors did not develop in mice receiving estradiol benzoate or testosterone propionate nor in the unilaterally gonadectomized mice.   Treatment with progesterone was not effective.

In 17 mice treated with progesterone, 8 granulosa cell tumors, one luteoma and 3 mixed cell tumors were found.   Metastasis of 1 granulosa cell tumor into the liver in 1 male castrated mouse was observed.   Microscopic examination showed that the tumor was encapsulated and composed of compact masses of granulosa cells showing mitotic figures.   In the liver each large solitary granu-

losa cell mass exhibited histologically a miniature of the primary tumor in the spleen.

This tumor was transplanted into 13 castrated mice and 4 weekly injections of progesterone were given. Progressive growth of the transplanted tumor in 1 female and 2 male mice was noted. The female was killed 73 days after the transplantation and tissue from this tumor was inoculated into 10 more castrated mice but progesterone was not given. The second transplant grew rapidly in all.

The author concludes that granulosa cell tumors induced in intraplenic ovarian grafts may become malignant growths. 5 figures.

(The experiments reported in this short paper, together with previous studies of the same author in collaboration with Gardner (Cancer Research 7: 38, 1947; Science 105: 13, 1947), represent one of the most interesting and most provocative developments in the study of the so-called dysontogenetic group of tumors. It is amazing to think that a genuine granulosal tumor, with or without luteinization, will often develop in ovarian grafts into the spleen, or for that matter the pancreas as well, of castrated animals. That these are genuine tumors is indicated by the fact that they continue to grow, that they metastasize, and that they can be transplanted into other animals. Moreover, they do not regress after progesterone administration, as do such estrogen-induced tumors as the fibromata produced by Lipschütz and his coworkers in guinea pigs.

The essential point in the production of these experimental granulosal tumors is that the ovarian tissue be implanted in the portal area, the obvious explanation being that the liver, in keeping with much available evidence, inactivates the estrogen produced in the grafts. Just why this should produce tumors is not known, and the hypothesis which the author suggests, that it is an unopposed FSH effect which is important, seems unsatisfactory, since there is certainly no evidence to indicate that the FSH principle, whether opposed or unopposed, is tumorigenic.

The suggestiveness of this new observation is all the greater when one places it beside the equally important demonstration by a group of investigators some years ago (Furth and Furth; Geist, Gaines and Pollack; Traut and Butterworth) that similar granulosothecomatous tumors develop in the ovaries of lightly irradiated mice. Both sets of observations add greatly to the evidence available from purely embryologic and histologic study that tumors of this type are to be explained by the differentiating potency of the gonodal mesenchyme. The original concept of Meyer that redundant granulosal rests are responsible for granulosa cell tumors is no longer adequate, and it certainly does not explain thecomas. But from the progranulosal and prothecal mesenchyme tumors may arise which are either granulosal, thecal or a mixture of both.

For that matter, the primitive gonadal blastema is the mother tissue not only of the characteristic ovarian constituents, both epithelial and connective tissue, but it is also the progenitor of all the testicular elements as well, so that it may equally well be the source of the masculinizing group of tumors which histologically is characterized by efforts at reproduction, usually in very imperfect and abortive fashion, of such testicular elements as sex cords, seminiferous tubules and interstitial cells. For that matter, there are some, like Teilum (Acta Obst. et Gyn. Scandinav. 24: 480, 1944), who believe that the adrenal cell or hypernephroid lipid cell tumors of the ovary, also masculinizing, are really interstitial or Leydig cell tumors, though the evidence for this view is far from complete.

I make these few comments simply to indicate the far-reaching applicability in the field of human oncology of the two new lines of approach which have been developed, and which may conceivably do much in the later clarification of our still very incomplete knowledge of the so-called functioning tumors of the ovary.—Ed.)

GIGANTIC OVARIAN CYST DEVELOPING IN A THECOMA

W. C. REINER

Portland, Oregon

Large ovarian tumors have become a rarity in civilized countries. The author reports the following case because of the infrequency of thecomas undergoing massive cystic degeneration and because of the method used in decompressing the tumor without spillage into the peritoneal cavity.

A 62-year old woman was admitted to the hospital because of a huge abdominal swelling of four years' duration. She was unable to lie on her back or to walk without great difficulty. Extending from the xiphoid process to the pubis was the abdominal mass. Her body was white and emaciated. Pelvic examination revealed the bladder protruding from the vagina and a bloody discharge from the vaginal opening.

The patient was given frequent feedings of nourishing food supplemented by cevitamic acid, vitamin K and crude liver extract. Under local and then general anesthesia an incision of 4 to 6 cms. was made in the midline below the umbilicus. The tumor thus exposed, the peritoneum and the rectus sheath were firmly sutured to the wall of the cyst. An empyema tube was then inserted into the cyst and secured, and 6000 cc. of brownish liquid were drained off. After this the tumor was slowly decompressed for 3 days. It was noted that too rapid decompression of the cyst resulted in a marked drop in the blood pressure even during a transfusion.

Three days after the draining a long midline incision was made and the tumor mass exposed. There were dense adhesions all over the entire cystic wall. The tumor was dissected free and removed.

This specimen was in a collapsed state and weighed 13½ lbs. Microscopic examination revealed that the tumor belonged to the class of solid ovarian neoplasms and the cyst formed as a result of thrombosis, necrosis, hemorrhage and disintegration of the blood. The cytology of the cells, showing a yellowish color and containing fat, favored an origin from the theca cells. Despite its size the tumor was still benign.

The patient made an uneventful recovery and left the hospital in good health. 4 figures.

(As the author states, it is certainly unusual for a thecoma to reach such enormous size, or for it to undergo such almost complete cystic degeneration as was evident in this particular case. It is sometimes difficult to form an opinion from published photomicrographic illustrations, but one would be justified in leaning away from the diagnosis of thecoma in view of the usually moderate size of thecomas and their generally solid consistency, although secondary cysts may at times be noted.

Pretty much everyone is agreed as to the advisability of removing even large cysts without preliminary tapping if this can be avoided, as it almost always can. There are occasional cases, however, in which, less often because of the large size of the cyst than because

of its fixation by adhesions and the reasonable certainty that manipulation would rupture the thin walls, a deliberate preliminary tapping is justified, always with every precaution to avoid spill, with its hazard of peritoneal implantation of tumor cells. Even histologically benign cystadenomas may carry this hazard, though it is of course greater with the malignant group. And the surgeon is often uncertain, from the external appearance of the cyst, whether its contents are benign or malignant.

In the case of huge ovarian cysts, which fortunately are usually non-adherent, it is safer to make a very long incision, even though it stretches from the ensiform to the pubes, than to risk leakage of the contents into the peritoneal cavity. Incidentally, these long incisions will look much shorter after involution of the overstretched abdominal wall is complete. From the author's description of his case, it does seem that some form of gradual decompression was justified, but such cases must be exceedingly uncommon.—Ed.)

FEMALE UROLOGY

THE DIFFICULT CASE OF STRESS INCONTINENCE

T. L. CHAPMAN

Victoria Infirmary, Glasgow

This writer reports the results of a fascia lata sling operation in 5 cases of stress incontinence of urine. The operation employed is a type which has not been much used; it is a variety of the operation described by Aldridge (1942).

An incision is made over the lower urethra and a channel is formed partly by sharp, and partly by blunt dissection on the lateral aspects of the urethra behind the pubis, reaching the deep aspect of the abdominal wall. A short transverse incision is made about an inch above the pubis, and stab wounds are made through the rectus sheath and muscle to connect with these channels. In this blind dissection no large vessels are encountered. A certain amount of hemorrhage may be expected in some cases, however, and a solution containing 10,000 units of thrombin should therefore be poured into each channel. It is obvious that infection must at all costs be avoided, and with the thrombin a mixture of antibacterial agents has also been used.

A graft of fascia lata is cut about 10 inches long and one inch wide. This is folded on itself with the smooth surface facing outwards, and a few stitches are inserted to make a structure resembling a tendon. The 2 ends of this graft are drawn up from the vagina to the abdominal wall and stitched over the rectus sheath. The graft is very strong, and by its tendon-like form it seems likely that it will retain its mobility longer than any other form of graft. A small catheter is inserted and the wounds are closed. Perhaps the most important point in performing this operation is to obtain the correct amount of tension on the sling.

Five cases are reported, with a good final result in each case. This operation has not a wide application, but can give relief where simpler measures have failed; the failure of these is the chief indication for its use. 6 figures.

(This operation utilizes the sling procedure employed in the better known operations of the Goebell-Stoeckel, Aldridge and Studdiford types, but differs from them in that it makes use of free strips of fascia lata instead of attached strips of the abdominal fascia. The latter would seem to be less likely to be followed by necrosis or sloughing, although the author's own results have been good thus far. As he states, it is only in the occasional case of stress incontinence, and more particularly in those in which simpler urethroplastic procedures have been unsuccessfully and perhaps repeatedly tried, that the sling type of operation has to be considered.—Ed.)

A UROLOGIC AND GYNECOLOGIC PROBLEM: CASE REPORT

B. M. HANCE

Easton, Pennsylvania

Urol. & Cutan. Rev., 52: 21–22, 1948

A 28-year-old woman consulted the writer 3 weeks after delivery with the complaint of being able neither to hold her urine nor to void. Cystoscopic examination showed that the distance from the base of the sphincter to the ureteral orifices was unusually long. There appeared to be a ridge anterior to the ureteral ridge and a depression between this ridge and the base of the sphincter. There was a tear in the internal sphincter at 3 o'clock. The urine contained albumin and pus cells. A urethrocele and first degree cystocele were present.

After 2 weeks of medical treatment, the urine became clear and operation was performed. By palpation, the ridge mentioned previously was brought forward and was stitched with interrupted chromic catgut to the base of the sphincter until the writer had restored the normal relation of trigone and sphincter. The sphincter was then repaired at 3 o'clock, because if the sphincter had been tightened at the base as is usually done in a Kelly operation, it would have only pulled the sphincter farther apart. Next, the vesico-vaginal septum was brought together until all evidence of urethrocele and cystocele had disappeared.

An indwelling catheter was kept in place for 10 days. After its removal the patient still could not void, so she was catheterized for 2 days, after which she began to void and was discharged. Two weeks later she had perfect control of urine.

Two months later the patient complained of painful coitus, and the author realized that she had a ureteritis. The renal pelves were irrigated with one per cent silver nitrate weekly for 4 weeks. From that time the woman had been completely symptom-free.

(It is probable that if more patients were cystoscoped within a few weeks of delivery than is actually the case, the incidence of such conditions as found in this patient would be much higher than might be expected. A good many of them would, after complete involution, present as cases of cystourethrocele, and in those in which operation is necessary, good results would as a rule follow urethroplasty by some such technic as that of Kennedy, with often also the Kelly plication method, not employed by Hance in his case. Since in the latter a definite tear of the internal sphincter was demonstrable, it was probably a good plan at that time to repair the torn sphincter. The postoperative use of the indwelling catheter in such cases is of importance, as is later catheterization until the bladder regains its tone, as determined by the absence of residual urine after catheterization.—Ed.)

OPERATIVE GYNECOLOGY

HYSTERECTOMY; A STUDY BASED ON 266 PERSONAL OPERATIONS PERFORMED IN 1945 AND 1946′

L. E. PHANEUF

Carney Hospital, Boston, Mass.

This paper concerns a series of 266 hysterectomies performed by the author in 1945 and 1946. Of these, 213 were abdominal and 53 were vaginal procedures. In the group of 213 abdominal hysterectomies, 88.7 per cent were total, and 11.3 per cent were cesarean, fundic and supravaginal hysterectomies. In the group of 53 vaginal hysterectomies, 86.7 per cent were complete, and the remaining 13.3 per cent were divided between the composite operation and vaginal supracervical hysterectomy.

According to these figures, the writer is now doing more than twice the number of panhysterectomies that he was doing 15 years ago. At the present time the total operation is done routinely, and the subtotal operation is reserved for special reasons or indications. Under present-day conditions the mortality of panhysterectomy, in experienced hands, should not be greater than that of the less formidable procedure.

In this group of 266 patients the ages were as follows: between 20 and 29 years, 10 patients; between 30 and 39 years, 63 patients; between 40 and 49 years, 125 patients; between 50 and 59 years, 46 patients; between 60 and 69 years, 17 patients; and between 70 and 79 years, 5 patients.

The principal diagnoses were as follows:

Uterine pathology:	Cervix:	Malignant	4
		Benign	11
	Corpus:	Malignant	6
		Benign	189
Ovarian pathology:		Malignant	2
		Benign	30
Tubal pathology:		Malignant	0
		Benign	16
Miscellaneous:			4

In connection with the 266 principal operations, 411 concomitant operations were performed: 260 of these were of a gynecologic nature, and 151 were of a nongynecologic nature. The adnexa were completely or partially removed in a total of 173 patients.

General anesthesia was given in 65 per cent of patients, and spinal anesthesia

in the remainder. Drainage was instituted in 32 abdominal hysterectomies. Sulfanilamide powder was left in the pelvis in 104 cases of abdominal hysterectomy and omitted in 109 cases. Transfusions were given pre-, intra- and postoperatively to 103 patients in this group; 50 were transfused with whole blood and 53 with plasma.

There were 3 deaths in the 266 patients, a gross mortality of 1.1 per cent. One death occurred after a panhysterectomy and 2 after supravaginal hysterectomies.

(The fact that 88.7 per cent of the author's abdominal hysterectomies were of the total variety indicates that he prefers the total technique, but that at times he, like all conscientious operators, feels that discretion is the better part of valor and that the hazard of the total operation in some cases would definitely outweigh the disadvantages of the subtotal. In former years many employed routine vaginal drainage after total hysterectomy, but most of us now use it only for some special indication. Local sulfanilamide likewise is being used less and less by abdominal surgeons, since it appears established that any benefit from it is due to its absorption into the circulation and not to any local effect upon infectious organisms. See also comment on following abstract of paper by Ottley.—Ed.)

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HYSTERECTOMY FOR NON-MALIGNANT CONDITIONS

C. M. OTTLEY

New Sussex Hospital for Women, and the Marie Curie Hospital

Opinions differ as to whether, when hysterectomy is to be done for non-malignant conditions of the uterus, the complete or the subtotal operation should be performed. A study of 2 groups of consecutive operations, comprising respectively 300 subtotal and 300 total hysterectomies carried out at the New Sussex Hospital, shows that 2 patients died in each group, giving a mortality rate of 0.66 per cent for each type of operation.

The author discusses the possibility of cervical stump carcinoma when subtotal hysterectomy is performed. Pearce estimates the incidence of stump carcinoma to be 1 per cent; Meigs has found an incidence of 0.73 per cent. Undiagnosed carcinoma of the cervix may be present at the time of subtotal hysterectomy, or primary carcinoma may arise later. Sarcomatous metaplasia of a fibromyoma is another possibility. The cervix, being but part of the uterus, is liable to share in any of the non-malignant conditions for which hysterectomy is done. In the writer's last 100 cases of total hysterectomy for non-malignant conditions, only 2 cervices showed a normal histologic structure. Sixty-six showed inflammatory infiltration; 47 showed fibrosis; 28, atrophic mucosa; 10, ovula Nabothii; 9, congestion; 5, mucous polypi; 3, dilated glands; and 3, erosion. It is a fair assumption that at least some of these cervices would have given trouble.

The complete operation is somewhat more lengthy and can be much more

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TOTAL HYSTERECTOMY BY DECORTICATION—CONCERNING 120 OBSERVATIONS

P. Figueroa Casas

Rosario, Argentina

Obst. y Ginec. Latino-Amer., 5: 649–651, 1947

The various arguments pro and con total and subtotal hysterectomy for benign lesions of the uterus are discussed by the author. Although the gynecologist should whenever possible choose conservative technics, there are many instances in which he has to resort to those more radical procedures. And in such circumstances, total hysterectomy seems to be the elective procedure for the following reasons: 1) removal of the danger of cancerization of the cervical stump, a complication which seems to be more frequent than the actual statistical reports reveal (1 per cent); 2) removal of a frequently pathological cervix, including chronic cervicitis, polyps, lacerations and other lesions which are quite often associated with myomas and other conditions requiring hysterectomy; 3) total drainage through the vagina, which obviously represents a great advantage.

The following facts have been presented as arguments against the performance of total hysterectomy; 1) a more difficult operation in which there is greater danger of postoperative hemorrhage. However, through comparative studies, it seems that this procedure merely requires a more meticulous hemostasis than the subtotal. 2) Shortening and abnormal dryness of the vagina accompanied by dyspareunia. This complication should no longer be feared, since it is more apt to occur following bilateral oöphorectomy, which is frequently accomplished along with total hysterectomy. Moreover, it is never observed following the decortication technic. 3) Alteration of the pelvic statics with vaginal prolapse as result. The latter is avoided by suturing the different ligaments which are encountered around the cervix as well as the broad, round and utero-ovarian ligaments onto the vaginal stump. On the other hand, even in subtotal hysterectomies there can occur prolapse of the cervical stump. 4) Danger of infection through the vaginal opening. There is less probability of infection when total hysterectomy is performed following thorough cleansing of the vagina, than when the subtotal operation is carried out, as during the latter the surgeon cuts through infected cervical glands. 5) Urinary complications, such as cystitis, pyelonephritis, vesico-vaginal and uretero-vaginal fistulas. The complications of infective nature are usually of mild degree and respond to antibiotic treatment; furthermore, they are also observed with subtotal hysterectomies. The traumatic complications in the bladder and ureters, although they really exist with the classic total technic, do not occur when the decortication technic is utilized. 6) Rectovaginal fistulas. These are due to rectal adhesions maintained by inflammatory conditions which, as a matter of fact, can occur with either type of operation. 7) Cancerization of the vaginal scar. There has been much confusion as to the incidence of cancer of the vaginal stump following operations for cancer of the cervix or of the uterine body, and that appearing after hysterectomy

difficult than the subtotal, especially when large fibroids are present or when the patient is very fat.   For these reasons, subtotal hysterectomy may be preferred when the patient is a poor surgical risk.   In the total operation it is important to keep the dissection quite close to the uterine wall and, by stopping all bleeding at once, to work in a dry field.   These precautions minimize the danger of injury to the ureters and neighboring structures.   In the present series no instance of such injury occurred among the total hysterectomies.   By cutting through the vaginal wall at its junction with the cervix it is possible to avoid shortening of the vagina.   If it is thought desirable to anticipate the possibility of prolapse of the vaginal walls, the round ligaments can be stitched to the cut edges of the vagina.

It is concluded that the advantages which must be conceded to total hysterectomy are not outweighed by any additional risk as compared with the subtotal operation when the patient is in reasonably good condition.

(This paper, as have an increasingly larger proportion of those of recent years, urges the superiority of total over subtotal hysterectomy.   The discussion on this point has been waged for many years, but the total hysterectomists appear to have been left in possession of the field.   On the other hand, it would be silly and rash for even the most experienced and expert gynecologist to insist on doing the total operation without exceptions.   He should, in the interests of the patient, be willing to settle for the subtotal operation in the minority of patients whose general or pelvic conditions would make the total procedure far more difficult and clearly more hazardous.   The increasing popularity of panhysterectomy means that more and more of our hospital residents will become trained in its technique, which was certainly not the case formerly.   For the surgeon not so trained, and for the occasional operator, it would probably be safer for the patient if the subtotal technique were followed.

Figures as to the incidence of stump cancer vary a good deal, but the hazard is a real one, and every gynecologist of experience has seen a good many such cases.   In a not inconsiderable proportion of these, the cancer was present in the cervix before the hysterectomy, in either precursory or active form.   It is the duty of the surgeon, if he contemplates leaving the cervix, to convince himself by meticulous examination, sometimes including biopsy, that this is not the case, and to correct, by such procedures as cauterization or conization, the simpler irritative lesions generally accepted as predisposing to cancer. This, however, does not compare in its protective value to the patient with removal of the cervix.   A patient simply cannot develop cervical carcinoma if she has no cervix, but she can do so in a retained cervix even though it has been treated, or even if it has never been the seat of demonstrable pathology.   This is entirely apart from the fact that retained cervices are not infrequently the source of discharge or bleeding which will worry both the patient and her doctor.—Ed.)

MISCELLANEOUS

STERILIZATION FAILURE WITH EXTERNAL MIGRATION OF THE OVUM

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The authors point out that there are numerous methods of tubal sterilization but that few of them have withstood the test of time without some failures. In the last 5-year period the writers have employed the double tubal ligation of short loops, following the technique of Norman Miller of Ann Arbor. They have encountered one failure and the present case, which was a suspected failure.

The case reported is that of a 40-year-old white female who was first seen in 1938. She had had a right salpingo-oophorectomy and appendectomy in 1933. Two previous pregnancies had terminated with dead babies, and a tear during this second delivery had resulted in a rectovaginal fistula. In 1939 and again in 1944 she was delivered of a living child by elective low cervical cesarean section. After her second cesarean section, sterilization was performed by ligation of 2 loops of the left tube. In 1945 she again became pregnant and obtained an induced abortion. Subsequently, she returned to the authors for repair of the rectovaginal fistula and resterilization. Difficulties encountered during the operation necessitated the performance of a vaginal hysterectomy and a left salpingo-oophorectomy. The patient made an uneventful recovery and was finally adequately sterilized.

Examination of the left tube by injected opaque media into both the uterine and fimbriated end showed it to be non-patent. Serial section confirmed the fact that continuity of the lumen was interrupted by the formation of fibrous tissue. However, serial sections taken through the right cornu of the uterus demonstrated the interstitial portion of the right tube to be patulous. Therefore, the ovum either before or after fertilization entered the uterine cavity through the patent interstitial portion of the right tube.

for benign conditions. We must admit that this complication is not more frequent than the primary cancer of the vagina. 8) Higher operative morbidity and mortality rates. However, statistics tend to show that the average incidence of such complications is about the same for both types of operation.

By utilizing the technic described by Lahey in 1923, the author has accomplished 120 total hysterectomies followed by one death only (0.85 per cent) and one vaginal hemorrhage which was promptly controlled by tamponade.

(The author of this paper, a well known South American gynecologist who has recently visited some of our American clinics, presents the pros and cons of the total vs. subtotal hysterectomy question fully and fairly. His conclusion that the total operation is the one which should be preferred is in accord with increasingly general opinion, and this would apply to the usual technic of panhysterectomy even without invoking the "decortication" technic, in which a rind of cervical muscle and fibrous tissue is left behind, a feature which is not considered by most surgeons as desirable or as essential to the safety of the operation.—Ed.)

AN IMPROVED OPERATIVE TECHNIQUE FOR SALPINGOSTOMY

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The author cites the justifiability of salpingostomy in certain cases, and describes a technique in which preparatory to laparotomy, air is forced into the uterus at a high pressure, and salpingostomy is then performed on the tube over the area of maximum crepitation.

With the patient anesthetized, one more insufflation is attempted to determine tubal patency. Air is forced into the uterus and maintained at a pressure of 225 mm. Hg for 2 minutes. If this test fails the abdomen is opened. Often, on palpating the tubes, crepitus will be obtained in one or both, proximal to the "block" which obstructed the distal flow of air at insufflation. If the tube is incised along its free border at the point of maximum crepitation, a new ostium can be established. When this is done, a mixture of air and "tubal content" gushes forth. As the insufflated tubal wall is thin and avascular usually, the bleeding is slight. The fashioning of the ostium may be left to the ingenuity of the surgeon. Fine silk or gut on an atraumatic needle is advised. Any unnecessary separation of adhesions should be avoided. The artificial opening should be established near the ovary, if possible, but the adnexa should not be roughly handled. Nor need the patency of the tubes be tested from above by traumatic procedures. The gush of air when the lumen is opened is ample proof that the tube is patent.

The author reports 3 cases in which the described procedure was employed. In each case, pregnancy followed within a year. These results seem to indicate the value of the method. 1 figure.

BOOK REVIEWS

On the Relation between the Thyroid Gland and Uterine Myoma. By Mauri Rouhunkoski. pp. 82. Mercatorin Kirjapaino, Helsinki, 1948. Also published as a supplement to Acta Obst. et Gyn. Scandinav., 28: 1948. The author's incentive for this study appears to have been derived from the still doubtful hypothesis that uterine myoma may be of endocrine causation, and the generalization that disordered function of one endocrine gland produces disturbances in other links of the endocrine mechanism of the body. This latter observation is probably true in a general way, but endocrinologists are stressing it less and less. Certainly in pretty much all the well-established endocrine syndromes, such as Graves' disease, the Cushing syndrome or acromegaly and gigantism, to mention only a few, it has been possible to put the finger on the ailing endocrine organ fairly precisely, regardless of minor secondary endocrine repercussions which are often associated. The endocrine therapists have likewise pretty well abandoned the gunshot pluriglandular methods once in unhappy vogue.

As for the possible estrogenic etiology of myoma, it appears to the reviewer that Rouhunkoski's summation of the evidence has not been as critical as it might be. For example, she does not question the applicability of Lipschutz's work to this question, in spite of the fact that the experimental tumors produced by this investigator and his collaborators are not myomas at all, that they do not involve the uterine wall but the pelvic connective tissue elements, and they are difficult to produce except in one species of animal, the guinea pig.

However, the studies of Rouhunkoski on a series of 100 unselected consecutive cases of uterine myoma are based on methods which appear to be as nearly objective as possible. She found that 39 of the women either exhibited or had had an enlarged thyroid, and, rather surprisingly, that the incidence of goiter in the nonparous group was higher (50.0 ± 7.2 per cent) than in the parous (28.8 ± 6.5 per cent). The basal metabolism was normal in 59 per cent of the entire group, increased in 29 per cent and decreased in 12 per cent, the normal values employed being −5 to +15 per cent. She studied also the complete blood pictures, the clinical symptoms, the total blood iodine, and iodine tolerance tests.

The fact that such a study as this has to envisage many variables is apparently recognized by the author when she expresses her impression that "a change has taken place in her country in the function of the thyroid during the war years."

She interprets her results as showing that a tendency to hyperthyroidism is not uncommon with myoma, though she appreciates that the age factor might have played some role in the final results. She finds no evidence of any special tendency to hypothyroidism in her series of cases.

On the whole, the results of this study appear to be very inconclusive and unimpressive. One wonders whether the findings in this series of cases would differ in any important way from those which would have been noted in a control series of 100 women with no myoma, with the same age distribution, coming from the

TRUE HERMAPHRODITISM

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As is well known, the sex of an animal depends primarily upon its genetic constitution, but for the full development of a functioning sexual animal the whole hormonal apparatus is essential. Hormones and other conditions can override the original sex chromosome and cause a sex-reversal. The writer discusses 3 groups of hermaphroditism: 1. True permanent hermaphrodites, in which ovary and testis remain together and function throughout life—e.g., earthworm. 2. Sex reversals in which the animal starts as one sex and passes through a hermaphrodite state to the other sex—e.g., the Buff Orpington hen. 3. Those individuals with the gonads and sexual apparatus of one sex and some or all the accessory organs and characters of the other sex—e.g., the mammalian intersexes.

Under group 3 come all those cases in mammals, including man, which although predominantly of one sex do nevertheless exhibit certain characters of the other sex. In the case of the freemartin, this is due to the earlier elaboration of the male sex hormones by the male twin *in utero*. Goldschmidt's theory suggests that sex and intersexuality are largely determined by a balance or lack of balance in the strength of the female genes.

lide, but that the specific lesion caused by the bacillus of tuberculosis should be designated as "tuberculous."

Even the experienced specialist will enjoy Dr. Ricci's book, if for no other reason because I believe we all like to know how our colleagues think and work. Moreover, it can be read with profit by the student, not in place of a well-rounded textbook on gynecology, but as a supplement to the latter.

EMIL NOVAK

same localities, etc. Unfortunately, no control studies are included in the author's monograph.

EMIL NOVAK

DIAGNOSIS IN GYNAECOLOGY. A Classification of Gynaecological Diseases Based on Aetiology and The Clinical Logic for Diagnosis. By James V. Ricci, A.B., M.D. The Blakiston Co. Philadelphia and Toronto. p. 247.

The subtitle of this book probably expresses its purpose better than does the title itself. While it does include a considerable amount of discussion as to the diagnosis of gynecological diseases and disorders, the general impression which is left on the reader is that of a brief synopsis of gynecology, although the coverage is admittedly incomplete, and impresses the reviewer as not as well balanced as it might be. For example, there is, for a book of this size and scope, a disproportionately long discussion of anatomy and embryology, comprising 49 of the 247 pages. This section is excellent but, since the book unfortunately contains not a single illustration, will be of comparatively little value except as a supplement to corresponding sections in textbooks of anatomy or gynecology.

A similar lack of proportion is seen in a good many of the chapters. As an illustration, the discussion of sterility is limited to a mere enumeration, in one paragraph, of the steps recommended by Simmons for the examination of the sterility patient.

The author has quite a flare for tabulation and classification of diseases, symptoms and etiological factors, and this may be of value to the student who is anxious for a quick and capsular review of the subject.

The book has a distinctly personal touch, being obviously based largely on the author's own extensive experience. The views expressed are sound, although, as in any book with such an individual flavor, not all readers will be in accord with some of the author's opinions. As a very minor point, I was interested in his preference of the right hand for pelvic examination. The traditional use of the left hand has become almost the mark of the guild among gynecologists, whatever may have been the fallacies of the logic on which it was originally based—the fact that it left the right hand free for instrumentation and abdominal manipulation, the probably unsubstantiated fact that left-sided pelvic lesions are more common than those on the right, the theory that tactile sensation is much more highly cultivable in the virgin field of the left hand than in the right, etc. With full appreciation of the weakness of all these reasons I believe that most gynecologists will still stick to the left hand, and leave the right to general surgeons and general practitioners.

Another minor criticism can be made concerning the author's use of the adjective "tubercular" instead of "tuberculous." I remember that a great many years ago the late Dr. W. W. Keen, a great literary purist as well as a noted surgeon, expressed himself very vigorously on this point in the letter column of the Journal of the American Medical Association. He called attention to the fact that "tubercular" refers to the gross form of a lesion, such as a tubercular syphi-

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